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PATHOLOGIC LAUGHING AND CRYING

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The occurrence of affective responses, such as involuntary laughing or crying, associated with lesions of the nervous system has been the topic of several contributions. By pathologic laughing and crying we mean involuntary and uncontrollable attacks of emotional expressions as a result of a cerebral lesion or lesions. The few attempts at correlation of these emotional expressions on a neuroanatomic and physiologic basis in man have led to various interpretations. The problem is beset by many difficulties because in most instances the lesions are neither isolated nor limited to specific areas of the nervous system. This is especially true in the cases of cerebrovascular disease and multiple sclerosis with multiple and bilateral lesions, in which pathologic laughing and crying commonly occur. At times, however, these affective responses appear in case of cerebrovascular disease at the same time as, or soon after, the ictus. In such cases, with utilization of the other clinical symptoms, a reconstruction of the localization of the lesion responsible for the emotional manifestations may be of value. It is well to remember that the generalized atherosclerotic condition of the cerebral vessels, even in cases of single hemiplegia, may cause widespread disturbance in emotional expression.

In order to evaluate properly the part played by the centers and pathways involved, it was found advisable to group the cases of this disturbance, as far as possible, in accordance with the reconstruction of the clinical picture, the onset of the pathologic laughing and crying and the location of the significant lesion. As will be demonstrated, these affective responses are present with lesions at various levels of

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the nervous system, from the cortex to the medulla oblongata. Apparently, there are pathways which originate in the cortex and which are in intimate connection with the thalamus, hypothalamus, basal ganglia, mesencephalon and faciorespiratory nuclei. A lesion in any of these centers or along the course of the associated pathways may account for the appearance of these responses. The difficulty of the problem lies in the inability, at present, to produce experimental lesions in the human subject similar to those in animals. These emotions in man are more complex than in animals, and comparable experimental results in the latter cannot always be applied with accuracy to man.

The purpose of this contribution is to demonstrate that certain centers and pathways mediate the normal emotional expressions and feelings associated with laughing and crying. When one or several of these centers or pathways are interfered with deviation from the normal takes place. The manifestation of emotional expressions or feelings or their absence, either of which is considered pathologic, is the effect of the integration of a residual mechanism for these emotional feelings and expressions. The changes induced in the integration of this mechanism may be caused by either destructive or irritative lesions.

In addition to a neurophysiologic interpretation, an attempt, whenever possible, will be made to link these disorders with psychologic phenomena. The spasmodic outbursts of laughing or crying in the neuroses and psychoses certainly cannot completely be explained on the basis here set forth. Although these manifestations will have to be explained on psychologic grounds, their origin and their transmission most likely depend on the centers and pathways to be described. In some of the cases included in this presentation slight psychotic phenomena in the nature of defects of orientation and memory were shown. Although these defects were present, it was always possible to establish sufficient contact with the patients and to determine by questioning them that the laughing and crying were spontaneous and uncontrollable and were not stimulated by their own conscious thoughts or environmental situations.

From the nosologic point of view, the adjective "pathologic" should include all types of attacks. The attacks that are apparently unmotivated should be referred to as automatic, involuntary, spasmodic or spontaneous. Those which cannot be prevented, started or terminated by an act of will should be described as uncontrollable. The attacks occurring in patients with mental deterioration are referred to as purposeless.

Of a series of 53 cases in which this emotional disturbance was studied clinically, autopsy was performed in 33. In 26 there was vascular disease of the central nervous system. In the rest the following disorders occurred: tumors (6 cases), multiple sclerosis (6 cases),

amyotrophic lateral sclerosis (5 cases) and various neurologic disorders (10 cases). Only representative cases from each group will be described in detail.

The cases indicated in the accompanying tabulation were described, as far as could be done, in accordance with the location of the lesion.

Level of Lesion	No. of Cases
Cortical	6
Corticodiencephalic	25
Diencephalic	15
Mesencephalometencephalic	7
Total no. of cases	53

For purposes of clinical description, each patient was observed during one or several attacks and was asked the following questions: "Do you laugh only, or is there an alternation between laughing and crying?" "Has the nature of the affective response changed during the illness?" "Is the condition present when you are alone or in a group?" "Does an attempt to speak cut off the attacks?" "Have you any idea why you laugh or cry?" "Do you believe that the provoking stimulus is in your conscious thoughts, in conversation or in external situation?" "Are you able to start or stop these responses voluntarily or in response to a command?" "Do the laughing or crying recur immediately after temporary cessation?" "Can you give any reason for the outbursts?" "Do these attacks occur only while you are awake?" "Has any one told you that the attacks are present during sleep?" "Are you aroused from a sound sleep by the attacks?" Further questions were asked for the purpose of elaboration, in accordance with the individual case. An effort was made to obtain a sequential history of the changes in these emotional responses that took place throughout the illness.

METHOD OF PROCEDURE

Each brain was sectioned frontally or horizontally at intervals of 1 cm., so that no lesions of significant size could have been missed. Whenever possible, blocks from the areas of destruction, as well as above and below them, were embedded in pyroxylin and stained by the myelin sheath and cresyl violet methods. In many cases the entire brain was embedded in pyroxylin after sectioning and cut serially, at a thickness of 50 microns.

LESIONS AT THE CORTICAL LEVEL

Laughing and crying, expressions of the affective sphere, can usually be controlled, and are therefore under the regulation of the higher cortical centers. The psychic activity of the cerebral cortex is colored by the sensations experienced in laughing and crying. These affective

responses, which may have their origin in the cortex also, are probably mediated by way of the corticohypothalamic and hypothalamocortical pathways. In the cases to be described, involvement of the aforementioned centers or tracts removes the normal regulatory control of the cortex over the hypothalamus or thalamus. The changes in facial expression and respiration associated with pathologic laughing and crying indicate that this pathway descends into the mesencephalon and metencephalon, where it undoubtedly has connections with the central facial and respiratory pathways and their respective nuclei.

Bard,[1] who did extensive experimental work on the emotions, expressed doubt concerning the existence of pathways and stimuli of cortical origin, because no case of "emotional paralysis originating in a cortical lesion has yet been recorded." In addition to our cases, a few instances have been recorded which indicate that the cerebral cortex contains centers for the integrating mechanism of emotional expression. Mills [2] expressed the belief that the right midfrontal region is a center concerned with the expression of the emotions. After lesions of the sensory cortex in animals Bickel and Jakob [3] noted explosive involuntary movements. Hartmann,[4] on this basis, concluded that a defect on the afferent side through the optic thalamus was responsible for the release of involuntary affective responses. Lewandowsky [5] and von Monakow [6] expressed similar views. As in Bickel's experiments, the diseased sensory cortex in some of our cases may have been responsible for the appearance of these emotional responses. Papez [7] stated that the gyrus cinguli and hippocampus and their interconnections with the hypothalamus and anterior thalamic nuclei constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression. The type of emotional expression herein reported has not, so far as we know, been recorded as following disease of the gyrus cinguli or hippocampus alone.

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1. Bard, P.: The Neuro-Humoral Basis of Emotional Reactions, in Murchison, C.: Handbook of General Experimental Psychology, Worcester, Mass., Clark University Press, 1934, pp. 264-311.

2. Mills, C. K.: The Cerebral Mechanism of Emotional Expression, Tr. Coll. Physicians, Philadelphia **34**:147, 1912.

3. Bickel and Jakob.: Ueber neue Beziehungen zwischen Hirnrinde und hintern Rückenmarkswurzeln hinsichtlich der Bewegungsregulation beim Hunde, Abhandl. d. k. preuss. Akad. d. Wissensch. **35**:763, 1900.

4. Hartmann, F.: Die Pathologie der Bewegungsstörungen bei der Pseudobulbärparalyse, Ztschr. f. Heilk. **23**:256, 1902.

5. Lewandowsky, M. H.: Die Funktion des zentralen Nervensystems, Jena, Gustav Fischer, 1907, p. 162.

6. von Monakow: Gehirnpathologie, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, Alfred Hölder, 1897, vol. 1, pt. 1.

7. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

Although in none of our cases was such solitary involvement disclosed, the possibility of the existence of such centers may be considered. In 1 instance (case 4), in addition to involvement of the motor, temporal and parietal convolutions, there was implication of the hippocampus. Definite conclusions cannot be drawn from a single case. From our series of cases of cortical lesions, we are impressed with the fact that fibers for emotional expression may originate from the greater part of the cerebral cortex, especially the frontal, premotor, motor and sensory cortex.

CASE 1.—*Occlusion of branches of the left middle cerebral artery; oculogyric crises associated with dysesthesia and pathologic weeping.*

C. F., a man aged 51, in October 1928 experienced attacks of dimness of vision in the left visual fields followed by involuntary deviation of the eyes to the right, with some jerking to the left. This was succeeded by "an unpleasant, sleepy, pins and needles sensation" over the right side of the body, at times starting in the upper or lower extremities and including the face and occiput. During the attack the patient felt dizzy, and on rising staggered forward. The episode terminated in a bout of uncontrollable weeping. The attacks came on at any time of the day and lasted from two to fifteen minutes; at times there were several successive seizures. He was mentally clear during the attacks and carried on a normal conversation. He suffered from hypertension, which increased during the seizures.

Neurologic Findings.—Prior to an attack there were noted only a wider palpebral fissure on the right than on the left and slight nystagmoid twitchings on lateral gaze to the right. Shortly before a paroxysm the patient complained of dimness of vision and vertigo. There was no flushing or blanching of the face. The eyes were deviated to the extreme right and could not be moved to the left. There were slight nystagmoid movements. The pupils were dilated and fixed. One attack lasted over an hour. During the attack the plantar responses were absent, and the right abdominal reflexes were less active than the left; otherwise all motor responses were normal. The ocular deviation was followed immediately by convulsive weeping. Immediately after the attack he complained of a "pins and needles" sensation over the right side of the body, including the face and occiput. He was often awakened from sleep by the dysesthesia and inferred that there might have been a preceding attack of convulsive weeping.

Course.—In December 1928 there appeared incomplete left homonymous inferior quadrantic hemianopia, with normal blindspots. The diagnosis of a lesion involving the right upper lip of the calcarine fissure was considered. In January 1929, after one of the attacks, there developed complete loss of power of the upper and lower extremities, weakness of the right lower part of the face, deviation of the tongue to the left, thickness of speech, hyperactive reflexes on the right and absence of the right abdominal reflexes. The patient died on Jan. 13, 1929.

Autopsy.—The entire brain was cut serially in sections 50 microns in thickness. There was an area of softening in the left parietal region, along the left interparietal and parieto-occipital fissures, involving part of the postcentral and superior and inferior parietal gyri on the left and part of the optic radiations (fig. 1). The basilar artery was partially obliterated. A small area of softening was observed in the medial nucleus of the right thalamus. Two other areas of

destruction were present in the left and the right inferior occipital gyri, respectively. Sections of the pons and medulla oblongata showed nothing of note.

Comment.—The oculogyric spasms to the right, followed by subjective sensory disturbances over the entire right side of the body and the pathologic weeping, in this instance were probably caused by the lesion in the left parietal region. Ferrier,[8] in 1879, on an experimental basis, and Landouzy,[9] Grasset,[10] Wernicke[11] and Henschen,[12] on

Fig. 1 (case 1)).—Coronal section through the left stria ventriculi, showing an area of destruction of the left postcentral convolution.

8. Ferrier, D.: Localization of Cerebral Disease, New York, G. P. Putnam Sons, 1879, p. 58; The Functions of the Brain, ibid. 1886, p. 242.

9. Landouzy, L.: De la déviation conjugée des yeux et de la rotation de la tête par excitation ou paralysie des sixième et onzième paires, Paris, A. Delahaye, 1879.

10. Grasset, J.: De la déviation, en sens opposé, de la tête et des yeux, Semaine méd. **24**:153, 1904.

11. Wernicke, O.: Herderkrankung des unteren Scheitelläpschens, Arch. f. Psychiat. **20**:224, 1889; On Paralysis of Latero-Version, Arch. Ophth. **32**:163, 1903.

(Footnotes continued on next page)

clinicopathologic evidence, have shown that cortical contingents for conjugate deviation of the eyes exist also in the parietal and supramarginal gyri. Although the inferior and middle frontal convolutions are the main structures concerned with conjugate movements of the eyes and head, there is sufficient evidence that other parts of the nervous system participate in this mechanism. These authors expressed agreement that involvement of fiber descending from these structures to the peduncles will give rise to conjugate deviation of the head or eyes or both. Of interest is the possibility of the correlation of the centers for conjugate deviation with the centers concerned with pathologic laughing and crying. The lesion in the parietal lobe in this instance most likely was responsible for the pathologic weeping, since this response constantly followed the oculogyric spasms and the dysesthesia. The lesion in the medial nucleus of the right thalamus could not account for this phenomenon, since the subjective sensory disturbances were on the right side of the body. This case demonstrates that pathologic crying may be associated also with cortical lesions.

CASE 2.—*Telangiectasis of the right motor region; left hyperreflexia; purposeless crying and laughing.*

L. R., a woman aged 82, was admitted because of a fractured right femur. There was left hyperreflexia. She was somewhat uncooperative and petulant and given to episodes of purposeless crying and laughing, which had been present for only eight months prior to admission. Sufficient contact could be made with her to establish that she was not psychotic.

Autopsy.—The brain was normal except for the presence of numerous dilated and engorged vessels in the right motor region (fig. 2), such as are seen in telangiectasis. These vessels were lined by a single or several layers of endothelial cells, surrounded by collagenous tissue. The lumen was distended and filled with red blood cells. These dilated channels were not seen in other parts of the central nervous system. There was, however, moderate atherosclerosis of the cerebral vessels. Microscopic studies of the various cortical areas and diencephalon did not disclose any outstanding pathologic changes.

Comment.—It is to be appreciated that the condition of the cerebral vessels in a patient 82 years of age may interfere with the general functions of the central nervous system. The absence of these emotional expressions up to eight months before admission suggests that the telangiectasia in the motor region led to this disturbance.

CASE 3.—*Tumor of the frontal convolutions and corpus callosum; spontaneous crying and laughing.*

J. R., a man aged 48, suffered an injury to the head in 1934. Shortly afterward, jacksonian seizures of the right side of the face and right arm developed. In May 1937 there appeared headaches, lapses in memory, irritability and spontaneous laughing and crying.

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12. Henschen, F.: Ueber Geschwülste der hinteren Schädelgrube: Klinische und anatomische Studien, Jena, Gustav Fischer, 1910.

Neurologic Examination.—The patient was euphoric, and irritable, laughed and cried without reason, acted silly and was disoriented as to time and place. There were blurring of both disks and bilateral hyperreflexia with signs of involvement of the pyramidal tracts. Ventriculographic examination revealed distortion of the right ventricle and displacement to the left.

Fig. 2 (case 2).—Telangiectasis of the right motor region.

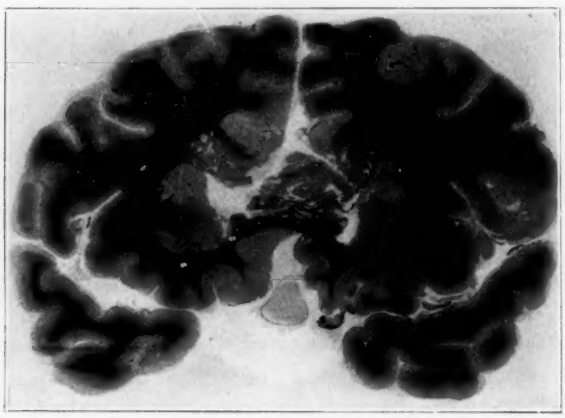

Fig. 3 (case 3).—Tumor involving the right frontal convolutions and the corpus callosum.

Autopsy.—A tumor nodule involved the right second frontal convolution and the greater part of the corpus callosum, including part of the splenium (fig. 3).

Comment.—This case demonstrates that pathologic laughing and crying may also occur with lesions of the second frontal convolution or corpus callosum. The former structure probably has contingents for

the control of this mechanism. This case further indicates that euphoria, silliness and irritability may be associated with outbursts of either laughing or crying.

CASE 4.—*Glioblastoma multiforme of the left motor, parietal, temporal and hippocampal convolutions; signs of left temporoparietal tumor, associated with uncontrollable crying.*

F. W., a woman aged 30, gave a history of severe right temporal headaches, nervousness, spontaneous crying spells, projectile vomiting and bilateral exophthalmos since June 1933. She was operated on for a tumor of the brain. After the operation she became quarrelsome and irrational. The crying spells continued.

Neurologic Examination.—There were left flaccid paralysis; impairment in position sense and astereognosis on the left; left supranuclear facial paralysis; involuntary crying spells; slight deviation of the tongue to the left, and gustatory hallucinations. The patient was uncooperative and euphoric. She described her periods of irritability and crying as attacks of nervousness over which she had no control. "They just come on, and I can't stop them." She was garrulous and rambling and had loss of insight and marked defect in memory and concentration in the later stages of the illness.

Autopsy.—A tumor, hemorrhagic in character, destroyed the motor, parietal, temporal and hippocampal convolutions and part of the pulvinar on the right.

Comment.—The crying spells in this instance resulted probably from involvement of the cortical contingents of the fiber tracts concerned with weeping, as most of the diencephalic structures, except the pulvinar, were spared. Compression or edema of the diencephalic structures by the tumor probably was not responsible for this affective response, as the condition persisted after the operation. The implication of the pulvinar as the cause of pathologic crying is not likely. The additional involvement of the hippocampus, as indicated by Papez,[7] suggests that this part of the archipallium may also send fibers concerned with emotional expression to the hypothalamus. This case was one of dissociation of emotional expression, uncontrollable crying spells, lack of control of feeling tone and euphoria with lack of insight.

CASE 5.—*Glioblastoma multiforme of the right premotor, motor, parietal and temporal convolutions; uncontrollable spells of crying, and occasionally of laughing.*

S. G., a man aged 51, had weakness of the left side and diminution of vision in 1928. After an operation in December 1928 for a right temporoparietal neoplasm power returned to the left side, but uncontrollable spells of laughing and crying appeared, often associated with spontaneous pains on the left side.

Neurologic Examination.—There were left hemiplegia, with signs of involvement of the pyramidal tracts; left supranuclear facial paresis on voluntary and emotional movements, and uncontrollable spells of crying, and occasionally of laughing. When asked about this, the patient said that he did not feel like crying but that he had no control over it. He died on Sept. 3, 1929.

Autopsy.—A tumor (glioblastoma multiforme), the size of an egg and containing two large cysts, had destroyed the right premotor, motor, parietal, temporal

and insular convolutions, the putamen, the external capsule and part of the internal capsule. The striatum, pallidum and thalamic and hypothalamic nuclei were compressed and edematous, and the third ventricle, which was constricted, was displaced to the left (fig. 4 *A* and *B*).

Comment.—In this instance it is impossible to state which of the cortical convolutions involved were responsible for the pathologic laughing and crying. There is every likelihood that the premotor, motor and

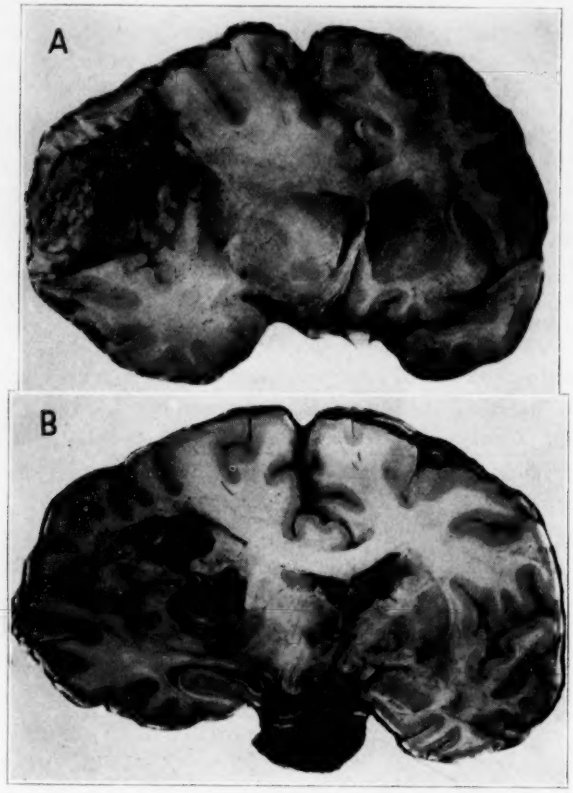

Fig. 4 (case 5).—*A*, tumor invading the right premotor and temporal regions, with edema of the right striatum and internal capsule. *B*, glioblastoma multiforme of the right motor, parietal, temporal and insular convolutions, compressing the thalamic and hypothalamic nuclei. There are distortion and narrowing of the third ventricle.

parietal convolutions give rise to fibers concerned with the control of this mechanism. That the compression or edema of the thalamic and hypothalamic nuclei should result in this affective response is also a possibility.

CASE 6.—*Tumor of the paracentral lobule, verified at operation; uncontrollable, automatic crying spells before operation; uncontrollable crying spells after operation, which later disappeared.*

J. M., a man aged 49, gave a history of increased irritability, forgetfulness, unmotivated and uncontrollable crying spells and paresis of the left side since November 1934. Shortly afterward there developed severe headaches, vomiting, failing vision, profuse sweating, with increased temperature of the left upper extremity, and inversion of the sleep mechanism.

Neurologic Examination.—The patient was torpid and drowsy. During the examination he had an attack of spontaneous crying. When aroused, he seemed euphoric and had no realization of the seriousness of his illness. There was left flaccid hemiplegia with pyramidal tract signs. All forms of sensation were diminished on the left side, with complete loss acrally. The fundi showed bilateral papilledema. The pupil and palpebral fissure were greater on the left than on the right. There was left supranuclear facial paresis.

Course.—In January 1935 a tumor from the right paracentral lobule and another just below it were removed. Shortly after, the spontaneous crying while the patient was alone disappeared. However, in the presence of the nurse crying spells occurred. These also disappeared, but the moment he saw some one else he cried. When his friends talked to him he cried, although the conversational content was apparently indifferent. When he listened the spells were less frequent than when he took part in the conversation. He often said to the nurse: "I feel foolish when I do that; I don't feel right doing it. I can't help myself. I don't know why I cry like that. Maybe I do it because I'm nervous." At no time was the mood appropriate before, during or after the crying. When he attempted to control the crying, his face was reddened, and he shed copious tears and sniffled. One morning, three weeks after the operation, he said to the nurse, with much determination: "I am not going to cry any more," and then had one outburst, but none subsequently. Occasionally, however, his eyes watered, and he blew his nose several times. The spontaneous quality of the crying spells finally ceased, but if he started to cry because of a sad event the weeping became uncontrollable. Within about five weeks after the operation this also disappeared. The spells occurred during the day or at night, although none were reported to have awakened him from sleep. There was no history of spontaneous laughing spells.

Comment.—It appears that normal emotional control may be absent and any stimuli, painful or otherwise, can evoke a crying spell. The explanation offered by this patient for the crying was similar to that of several other patients with diffuse cerebral lesions and mental hebetude. After the removal of the tumor the spontaneous outbursts disappeared, but the uncontrollable crying spells remained. In due time the patient could voluntarily control this weeping. This suggests that the paracentral lobule, with other parts of the motor and sensory systems, participates in the control of these affective responses.

LESIONS AT THE CORTICODIENCEPHALIC LEVEL

In contrast to the rarity of pure cortical lesions responsible for these affective responses, lesions involving the cortex and diencephalic structures are more frequently encountered. In many of these cases it will

be difficult to determine whether disease of the cortex or of the diencephalon alone or of both was the cause of the appearance of this form of emotional expression.

Nothnagel [13] postulated the presence of a "psychoreflex" facial pathway separate from the supranuclear facial component. According to him, the thalamus and its cortical connections are situated on this "psychoreflex" pathway.

Wilson [14] suggested that both the facial and the respiratory mechanism participate in the act of laughter and weeping. He postulated a "center linking the 7th nerve nucleus in the pons with the 10th motor nerve nucleus (nucleus ambiguus) in the medulla oblongata and the phrenic nuclei in the upper cervical cord." This faciorespiratory mechanism, according to Wilson, has a supranuclear voluntary control for inhibition of these automatic movements and an involuntary control for release of the expression of emotion. The voluntary action, he asserted, is controlled by the corticopontile, corticobulbar and corticospinal tracts, and lesions of the "geniculate bundle of the pyramidal tract anywhere in its course," especially bilateral lesions, as in cases of pseudobulbar palsy, will cause pathologic laughing and crying. The involuntary control over the automatic activity of the faciorespiratory mechanism, he stated, on the basis of Spencer's [15] investigation, is exercised by pathways originating in the cortex and descending separately to approach the midline in the regio subthalamica and tegmentum. Bard, however, on the basis of his experimental work, expressed disbelief in the cortical origin of these pathways. He concluded that strong emotions are subcortical and that the central mechanism lies in an area comprising the caudal half of the hypothalamus. He expressed the opinion that the complete expression of the affective responses depends on an intact hypothalamus. Fulton and Ingraham,[16] by making incisions in the brains of cats anterior to the optic chiasm, extending from the midline of the olfactory radiation, concluded that the rage responses in several animals were probably produced by the division of the corticohypothalamic pathway, thus releasing the hypothalamus.

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13. Nothnagel, H.: Zur Diagnose der Sehhügelkrankungen, Ztschr. f. klin. Med. **16**:424, 1889; Topische Diagnostik der Nervenkrankheiten, eine klinische Studie, Berlin, A. Hirschwald, 1879, p. 251.

14. Wilson, S. A. K.: Pathological Laughing and Crying, in Modern Problems in Neurology, New York, William Wood & Company, 1929, pp. 260-296.

15. Spencer, W. G.: The Effect Produced upon Respiration by Faradic Excitation of the Cerebrum in the Monkey, Dog, Cat, and Rabbit, Phil. Tr., London **185**:609, 1894.

16. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Prechiasmal), J. Physiol. **67**:xxvii, 1929.

CASE 7.—*Emboli in the right lenticulostriate artery and the branches of the left middle cerebral artery; recurrent attacks of pathologic laughter; cessation of the affective response, due to recession either of the lesion or of edema.*

S. P., a man aged 39, who suffered from chronic valvular disease and auricular fibrillation, had transient flaccid hemiplegia on the right and motor aphasia in 1931, which disappeared except for slight memory defect and inability to read what he had written. In 1932 there developed paralysis on the left side, associated with uncontrollable laughing. Any attempt to speak resulted in gales of laughter, which he could stop only temporarily. He felt foolish and ashamed, and had tears in his eyes because he could not "control the laughter." This disappeared in two weeks. On Dec. 7, 1934, there developed anarthria, dysphagia, left and partial right upper facial paresis, left palatal paresis, deviation of the tongue to the left and return of pathologic laughing with crying. The moment any one approached him he laughed so uproariously that he complained of pain in the chest; he could not stop laughing until the person had left him. Tears came to his eyes, although this was not his mood. The upper part of his face expressed sadness, the lower part laughter, while his true emotion was one of anguish. This condition persisted for four days; as soon as he was able to carry on a conversation the laughing disappeared.

Neurologic Examination.—Six weeks after the last attack there was left facial paresis at rest, on voluntary movement and on talking, but overreaction on emotional stimulation. The muscles of the right side of the face showed overreaction on talking and relative mimetic paresis. The palate was in the midline, and the tongue deviated to the right. There was affective lability, more often euphoria, with good feeling tone. He always had been of a rather morbid and worrisome nature. The mood was not pertinent to his actual life situation, and he showed lack of insight and poor judgement. He said he dreamed recurrently of an old enemy to whom he was giving a terrible thrashing. He laughed uproariously about this, saying he realized that in his present state this was impossible. He was aware of his recent memory defect. Remote memory and mental tension were good. Counting and calculation were fair. He was known about the hospital for his cheerfulness, being much sought by patients because of his ability to sing and play the guitar. He died after embolism of several cerebral arteries.

Autopsy.—There was an area of softening along branches of the middle and posterior cerebral arteries on the left, with involvement of the second frontal, precentral, postcentral, insular, inferior temporal, fusiform and hippocampal convolutions on that side. The internal capsule and putamen on the same side were also involved. There were, in addition, two small lesions in the left medial thalamic nuclei. Another area of softening destroyed part of the putamen and anterior part of the internal capsule on the right side.

Comment.—The lesion on the right side involving the internal capsule most likely accounts for the first episode of uncontrollable laughing. The second episode of laughter possibly was caused by an embolus in the left side of the brain, involving the motor cortex and internal capsule. The lesion in the left thalamus must also be considered as a possible causative factor in the laughter. The pathologic laughing and crying may also have been the result of the bilateral lesions. It was not clear whether the laughing ceased because of the recession of the lesion or of

the edema. That there was no disturbance of will is evidenced by temporary voluntary cessation of an apparent uncontrollable attack of laughter in this case. The patient's cheerfulness, in spite of a previous morbid point of view could not be attributed entirely to lack of insight, for his illness weighed less heavily on him than the responsibilities of which it relieved him. His reaction was suggestive also of mild hypomania, and with it complete denial of reality.

CASE 8.—*Multiple cerebrovascular lesions; bilateral occlusions of branches of the middle cerebral artery; left hemiplegia; uncontrollable laughing and crying.*

S. Z., a man aged 69, had had paresis and convulsions on the right side and unconsciousness in 1929. In March 1931 there developed left hemiplegia and spontaneous spells of crying and laughing.

Neurologic Examination.—There were left hemiparesis with bilateral pyramidal tract signs and right facial palsy on voluntary and mimetic movements. The patient was puzzled by his spontaneous, explosive crying spells, which occurred even in the midst of a pleasant conversation and at times awakened him from sleep. The spontaneous laughing spells, which appeared with the onset of the hemiplegia in 1931, lasted only for a few months; they always terminated in a happy mood, regardless of the initial state of mind.

Course.—Later, there developed a masklike facies, with bilateral facial paresis and normal mimetic responses. The facial reflexes were hyperactive, particularly on the left, with a marked, almost inexhaustible, sucking reflex. Mental examination revealed no abnormalities. The mood was normal before the attacks and happy as the laughing spell progressed and terminated, but the patient felt badly about the crying spells because they prevented him from talking. When questioned, he could not account for the onset of the laughing spells. During the examination he had many individual attacks of crying, which were elicited by any kind of stimuli As the examination progressed the type of stimuli causing them became fewer and seemed limited to those of a painful affective quality. The crying itself most often consisted only of pursing the lips, with a central round opening, and several rapid, short expiratory, almost toneless, grunts ("hoo-hoo"). The mouth at times assumed the appearance of a *Schnauzkrampf,* a reaction to sucking. The left eye closed first, then the right. The lips became retracted; the expirations were few, being limited by the lack of air caused by failure of an initial inspiration. The face became gradually reddish purple and remained immobile for about thirty seconds. Talking to the patient helped to end the attack.

Autopsy.—There were several areas of softening along the distribution of branches of both middle cerebral arteries, destroying on the right the premotor, motor, parietal, supramarginal and angular gyri and on the left the same convolutions as well as the second and third frontal gyri and the internal capsule and striatum (fig. 5 *A* and *B*).

Comment.—Of interest in this case were the associated sucking reflex, with the outburst of crying, and the differences in the mood of the patient when laughing and when crying. Adequate stimuli at times induced the crying spells. This is one of the few instances in our series in which an attack of abnormal laughter became associated with the requisite feeling tone as the attack progressed. Since he could not

explain the reason for laughing, we must assume that stimuli operating and not immediately available to consciousness induced the attack. The presence of emotional tension sufficient to awaken the patient from sleep, accompanied by an outburst of crying, further suggests that unconscious stimuli may provoke some of these attacks.

Spontaneous crying spells were much more frequent, and as the attack progressed they became associated with the requisite feeling tone. Because of their uncontrollable nature and their emotional content they made the patient feel sad.

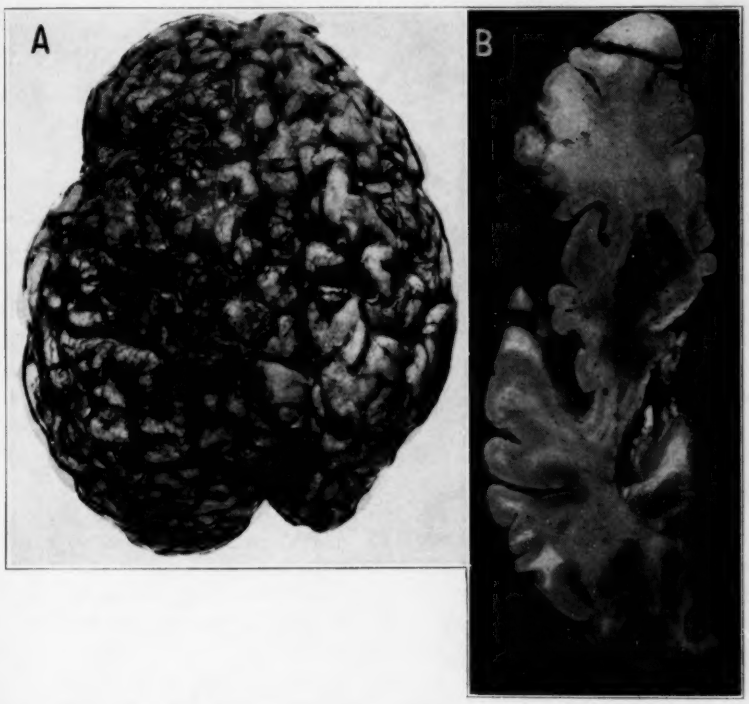

Fig. 5 (case 8).—*A*, bilateral areas of softening involving the premotor, motor and parietal convolutions. *B*, area of destruction in the region of the left striatum and internal capsule.

The subsequent feeling tone might be one of happiness because of the effect of the emotional expression occurring with laughter or one of sadness because the attacks were uncontrollable. The attacks limited his social contacts and prevented him from talking. These attacks, as in other instances (Wilson's case), led even to catalepsy. The lesion of the right cerebral hemisphere, which developed in 1931, with the onset of the left hemiplegia, possibly was responsible for the pathologic laughing and crying. Bilaterality of lesions, however, cannot be excluded.

CASE 9.—*Polycythemia; thrombosis of the left middle cerebral artery; hemiplegia; aphasia; uncontrollable crying spells and irritability.*

I. S., a man aged 47, who suffered from polycythemia, experienced hemiplegia and aphasia on the right side.

General and Neurologic Examination.—The patient was cyanotic and plethoric; there were marked sensory aphasia, right spastic hemiplegia, loss of all forms of sensation on the right side, engorgement of the retinal vessels, right supranuclear facial paresis and uncontrollable crying spells and irritability.

Laboratory Data.—The red cell count ranged from 7,500,000 to 8,500,000 and the hemoglobin content from 105 to 115 per cent.

Autopsy.—There was an area of softening along the distribution of the left middle cerebral artery, destroying the second and third frontal, the motor, the parietal, the superior temporal, the supramarginal and the angular gyri, the basal ganglia, the internal capsule and part of the thalamic nuclei.

Comment.—The uncontrollable crying spells in this instance resulted from involvement of the cortical contingents of the tract concerned with this mechanism, either at their point of origin in the cortical convolutions or in the diencephalic nuclei. Because of their uncertainty, this and the succeeding cases are grouped with those of lesions at the cortico-diencephalic level.

CASE 10.—*Schilder's disease; extensive demyelination of the white matter, diencephalic nuclei and internal capsule of the right hemisphere; pathologic laughing and crying; left supranuclear facial palsy, with overreaction on emotional expression and marked emotional instability.*

B. T., a girl aged 15, had presented convulsions, poor vision, mental retardation, silly and purposeless behavior, unprovoked and uncontrollable outbursts of laughing and occasional crying spells since 1928.

Neurologic Examination.—There were signs of involvement of the left pyramidal tract, with spasticity and athetoid movements of the left hand and a striatal position of the left foot. The patient walked with a broad base, with the left lower extremity abducted. She complained of smelling peculiar odors, such as ether. Visual acuity was poor; there was left homonymous hemianopia. The fundi showed bilateral primary atrophy of the optic nerve. There were left supranuclear facial palsy, with overreaction on emotional expression; marked emotional instability, and spontaneous laughing. Later there developed oculocephalogyric spasms to the left, with clonic movements of the left upper and lower extremities, twitchings of the face, nystagmus to the left and spontaneous flinging movements of the right upper extremity over the left shoulder and the back.

Autopsy.—The changes were typical of encephalopathia periaxialis diffusa (Schilder's disease), with almost complete demyelination of the entire white matter of the right hemisphere, partial demyelination of the white matter of the left hemisphere and preservation of the arcuate fibers (fig. 6). The white matter of the fiber system of the right putamen, globus pallidus and internal capsule and of the corpus callosum on the right side was markedly demyelinated. There was also slight demyelination of the right pontile fibers.

Comment.—The pathologic laughing and crying in this instance, which was associated with left supranuclear facial palsy and overreaction

on emotional response, may have been the result of involvement of the contingents of the faciorespiratory mechanism present in the white matter of the right cerebral hemisphere, in the diencephalic nuclei, in the internal capsule and possibly also in the corticopontile fibers. The multiplicity of lesions cannot be excluded as the cause of these attacks.

The following cases, which are abstracted in brief, are those in which autopsy was performed.

Case 11.—S. Z., a woman aged 54, had thrombosis of the left middle cerebral artery, aphasia, right flaccid hemiplegia, right supranuclear facial paresis when at rest and on emotional response, spontaneous outbursts of laughing and crying and irritability.

Case 12.—R. W., a woman aged 47, had thrombosis of both middle cerebral arteries, bilateral pyramidal tract signs, aphasia, apraxia, agraphia, alexia, left

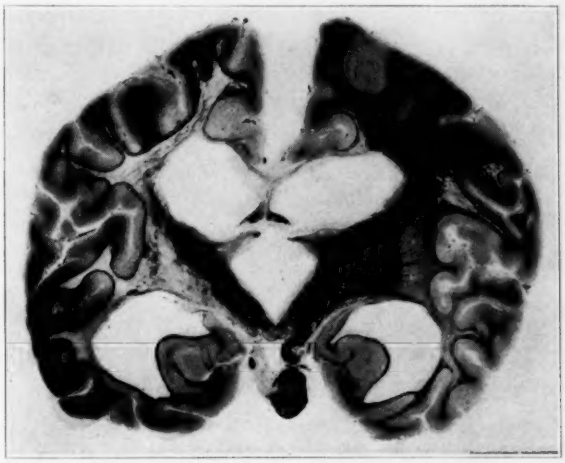

Fig. 6 (case 10).—Coronal section through the third ventricle in a case of Schilder's disease. There are demyelination of practically all the white fibers and internal capsule of the right hemisphere, with sparing of the arcuate fibers; thinning and demyelination of the corpus callosum and slight demyelination of the pontile fibers; patchy demyelination on the left side, and involvement of the right striatum and pallidum.

supranuclear facial paresis when at rest and on emotional response and spasmodic laughing and crying.

Case 13.—S. W., a woman aged 25, had malignant hypertension, thrombosis of the left middle and right posterior cerebral arteries and bilateral pyramidal tract signs. Subsequently there were aphasia followed by emotional instability; outbursts of laughter and weeping on the least provocation; temper tantrums without basis, and left supranuclear facial paresis, with overreaction on emotional response. Later the aphasia became global, and constant screaming was present.

Case 14.—J. T., a man aged 28, had malignant hypertension, thrombosis of branches of both middle cerebral arteries, right hemiplegia; spontaneous laughing

and crying; right supranuclear paresis when at rest and on voluntary movement, but overreaction bilaterally on emotional response.

CASE 15.—G. R., a man aged 67, had malignant hypertension, thrombosis of branches of the middle cerebral arteries with multiple vascular insults, paralysis of the left side, right supranuclear facial paresis with masklike facies and unprovoked laughing and crying, following the second vascular episode.

CASE 16.—D. M., a man aged 54, had thrombosis of the right middle cerebral artery followed by motor aphasia, left hemiplegia and spontaneous laughing and crying. The aphasia disappeared, but the crying continued. With subsequent vascular insults on the left side, the aphasia recurred but the emotional outbursts remained the same.

CASE 17.—G. M., a woman aged 60, had thrombosis of the left middle and branches of the right middle cerebral artery, bilateral pyramidal tract signs, motor aphasia, right supranuclear facial paresis, uncontrollable laughing and crying and emotional instability.

CASE 18.—M. B., a man aged 53, had thrombosis of branches of both middle cerebral arteries; bilaterial pyramidal tract signs; right supranuclear facial paralysis; violent, uncontrollable outbursts of weeping and laughing, after which he felt badly and feared people might think he was insane.

CASE 19.—R. B., a woman aged 55, had thrombosis of the right middle cerebral artery; left hemiplegia; global aphasia, and frequent outbursts of crying, with and without motivation. The outbursts were at times sudden in onset and in termination, and at times toneless, with or without tears.

CASE 20.—S. W., a man aged 26, had multiple sclerosis, with multiple plaques in the white matter of the cerebral hemispheres and in the diencephalon. The picture was typical of multiple sclerosis. There were uncontrollable, unmotivated or easily motivated outbursts of laughing and crying.

CASE 21.—A. A., a woman aged 35, had multiple sclerosis, with multiple plaques in the white matter of the frontal and occipital convolutions, thalamus, hypothalamus and internal capsule. The picture was typical of multiple sclerosis, with bilateral supranuclear facial paralysis. There were uncontrollable outbursts of laughing and crying.

CASE 22.—M. L., a woman aged 39, had multiple sclerosis, with multiple plaques in the white matter of the cerebral hemisphere, diencephalic nuclei and pons. There were excessive smiling, extreme facetiousness and euphoria. This case showed the relation of hypermimia to pathologic laughing.

The following are cases in which autopsy was not performed.

CASE 23.—S. F., a woman aged 45, had essential hypertension, thrombosis of branches of the left middle cerebral artery, right hemiplegia, motor aphasia and outbursts of crying.

CASE 24.—E. G., a man aged 56, had thrombosis of the left middle cerebral artery, right hemiplegia, mixed aphasia, supranuclear facial paresis with facial apraxia, explosive outbursts of laughing following relevant and irrelevant stimuli, euphoria and facetiousness. With the disappearance of the aphasia the laughing continued, and the patient's previous pleasing personality returned. Singing and

humming the operas, with which he was familiar, usually ended in an outburst of laughing. When he could not express a word he became disgusted, but was never irritated.

CASE 25.—J. M., a man aged 46, had thrombosis of the right middle and branches of the left middle cerebral artery, bilateral pyramidal tract signs, left flaccid hemiplegia and transient apraxia, left hemiparkinsonism, bilateral supranuclear facial palsy, a sucking reflex and mental deterioration. The expression was one of constant smiling and grimacing, with occasional spontaneous outbursts of uncontrollable laughter. Occasionally these were precipitated by appropriate stimuli and ended in a happy mood. The attacks could be stopped voluntarily and on command. He could never cry because, as he said, he "could not see a purpose in it." Apparently this indicated good insight, but he was too complacent about his illness.

CASE 26.—J. S., a man aged 63, had thrombosis of branches of both middle cerebral arteries, impairment of memory, motor aphasia, bilateral pyramidal tract signs, parkinsonism, paresis for volitional and mimetic movements of the left side of the face and outbursts of spontaneous laughing and crying. The mood seemed one of euphoria, although the patient stated that he felt sad. He smiled when he said he was concerned about his illness, but at no time did he shed tears.

CASE 27.—H. Z., a man aged 44, had thrombosis of branches of the anterior and middle cerebral arteries, mental deterioration, parkinsonism, pyramidal tract signs, weakness of the right side of the face on voluntary movements and in emotional expression, weakness of the left side of the face when at rest and spontaneous, uncontrollable laughing or crying, either of which changed to the other in the course of the attack.

CASE 28.—J. S., a man aged 56, had thrombosis of the right middle cerebral artery; complete left hemiplegia, with loss of all forms of sensation; left supranuclear facial paresis, at rest and on voluntary movement; mental deterioration, and frequent involuntary sobbing, accompanied by tears without sadness.

CASE 29.—M. G., a woman aged 38, had signs and symptoms of multiple sclerosis; loss of memory; paresis for volitional and mimetic movements of the face and outbursts of compulsive laughter. When laughing at something humorous she could not stop; the crying did not have this compulsive quality. She appeared silly and facetious, but true euphoria was not present. There seemed to be complete absence of feeling tone.

CASE 30.—J. S., a man aged 39, had typical multiple sclerosis, with euphoria and uncontrollable outbursts of laughter. Even when he wanted to cry he could only laugh.

CASE 31.—L. L., a woman aged 54, had typical amyotrophic lateral sclerosis; there were spontaneous, uncontrollable outbursts of crying, followed by a mood of sadness.

LESIONS AT THE DIENCEPHALON LEVEL

Pathologic laughing and crying have been described in cases of lesions limited to the diencephalon. In some of these cases lesions were observed in the thalamus, and the authors expressed the belief that perhaps this nuclear mass was the center for the affective responses. The question whether thalamic lesions, interruption of the cortico-

thalamic, corticohypothalamic pathways or secondary involvement of the hypothalamus by compression or edema was responsible for the release of these emotions is still debatable. In some of the cases the lesions were in the basal ganglia or the internal capsule, and the role played by these structures in the release of affective responses must be considered.

Weisenburg and Guilfoyle [17] described involuntary crying in a case of tumor of the thalamus. Compression of the hypothalamus in this instance had not been ruled out. It is well known that lesions of the thalamus may frequently be unaccompanied by these affective responses. Brissaud,[18] on the other hand, placed the lesion essentially in the "psychic pathway" of the anterior limb of the internal capsule and maintained that the thalamus must be intact for the production of involuntary laughter and weeping. This author [19] and Giannuli [20] reported cases of involuntary crying and laughing in which clinical observations were supplemented by autopsy material. In Giannuli's case, both thalami were involved, and in both instances there were lesions in other parts of the nervous system. Brissaud expressed the belief that these lesions were irritative and that the associated disease in the basal ganglia also may have played a role in this mechanism. Dupré and Devaux,[21] de Burzio [22] and others have described lesions of the putamen and internal capsule associated with involuntary laughing and crying.

Experimental and clinicopathologic studies concerned with the release of other affective responses may elucidate the role played by the hypothalamus or other diencephalic structures in the understanding of pathologic laughing and crying. Bard indicated that strong emotions, such as rage, are subcortical in origin and are probably dependent on the caudal half of the hypothalamus. He expressed the opinion that the full capacity of the affective expression depends on intactness of the hypothalamus. Prior to Bard,[23] Goltz,[24] Dusser de Barenne,[25] Roth-

17. Weisenburg, T. H., and Guilfoyle, W. F.: Tumour Destroying Most of the Optic Thalamus and Causing Central Pains, Vasomotor and Trophic Disturbances, Involuntary Howling and Deviation of the Body to the Opposite Side, Rev. Neurol. & Psychiat. **8**:325, 1910.

18. Brissaud, E.: Leçons sur les maladies nerveuses (Salpêtrière, 1893-1894), edited by H. Meige, Paris, G. Masson, 1895.

19. Brissaud, E.: Le rire et le pleurer spasmodiques, Rev. scient. **1**:38, 1894; Rire et pleurer spasmodiques, Rev. neurol. **8**:824, 1900.

20. Giannuli, F.: Riso spastica, Ann. d. Inst. psichiat. d. r. Univ. di Roma **4**:213, 1905.

21. Dupré and Devaux, A.: Rire et pleurer spasmodiques par ramollissement nucleocapsulaire antérieur: Syndrome pseudobulbaire par désintegration lacunaire bilatérale des putamens, Rev. neurol. **9**:919, 1901.

22. de Burzio, F., abstracted Rev. neurol. **8**:824, 1900.

23. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Especial Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

(Footnotes continued on next page)

mann [26] and Schaltenbrand and Cobb [27] showed that cortical ablation renders an animal excessively prone to the display of anger and other emotions. On the basis of these experiments, Bard expressed agreement with Hughlings Jackson's [28] view that decortication in these instances acted as a "release" of the subcortical rage mechanism from the cortical inhibitory influence.

Foerster and Gage [29] and others obtained manic-like reactions in human subjects by irritation of the hypothalamus in the presence of an intact cerebral cortex. Alpers,[30] in a clinicopathologic report, produced evidence that emotional disturbances may result from lesions of the hypothalamic nuclei. In his, as in Foerster's cases, the cerebral cortex was intact. This suggests that the hypothalamus also has an inhibitory influence on the cortex. Although the evidence brought forth shows that the hypothalamus is possibly one of the main centers for the control of affective responses, there are undoubtedly other centers (as demonstrated by us and others) which have to do with this mechanism. Our cases of disease of the thalamus and basal ganglia demonstrate that these structures must be in intimate connection with the hypothalamus and other centers for affective responses. Interruption of these pathways on their way to the hypothalamus or of the descending pathways from the hypothalamus may lead to the production of the same mechanism.

CASE 32.—*Invasive meningioma of the hypothalamus, thalamus, substantia nigra, cerebral peduncle and mesencephalon on the left; hyperthermia; lethargy; extrapyramidal symptoms; right hemiplegia; pathologic laughing and crying.*

B. S., a man aged 52, suffered in March 1932 for seven days from fever, with a temperature of 104 F., and lethargy. After this episode he became easily

24. Goltz, F.: Der Hund ohne Grosshirn, Arch. f. d. ges. Physiol. **51**:570, 1892.

25. Dusser de Barenne, J. G.: Recherches expérimentales sur les fonctions du systeme nerveux central, faites en particulier sur deux chats dont le neopallium avait été enlevé, Arch. néderl. de physiol. **4**:31, 1919.

26. Rothmann, H.: Zusammenfassender Bericht über den Rothmannschen grosshirnlösen Hund nach klinischer und anatomischer Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:247, 1923.

27. Schaltenbrand, G., and Cobb, S.: Clinical and Anatomic Studies on Two Cats Without Neocortex, Brain **53**:449, 1931.

28. Jackson, J. H.: Clinical and Physiological Researches on the Nervous System: I. On the Localisation of Movements in the Brain, London, J. & A. Churchill, 1875; The Croonian Lectures on Evolution and Dissolution of the Nervous System, Brit. M. J. **1**:591, 660 and 703, 1884; Neurological Fragments, Lancet **2**:128, 1893.

29. Foerster, O., and Gagel, O.: Ein Fall von Ependymcyste des III. Ventrikels: Ein Beitrag zur Frage der Beziehungen psychischer Störungen zum Hirnstamm, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:312, 1933.

30. Alpers, B. J.: Relation of the Hypothalamus to Disorders of Personality: Report of a Case, Arch. Neurol. & Psychiat. **38**:291 (Aug.) 1937.

fatigued, slept most of the time and complained of frequent headaches. In July 1932 there appeared drooping of the right side of the face, followed shortly by weakness of the right upper and lower extremities and dragging of the right lower extremity. Incontinence of urine, and at times of the feces, had been present since 1934. In 1935 there appeared diplopia and pain in the right shoulder. At about this time the family noticed that he laughed and cried for no apparent reason. In the past year he had been in coma for twelve hours on two occasions.

Neurologic Examination.—The patient was apathetic and somewhat lethargic. There were swelling of the right arm and leg, right spastic hemiplegia with increase in the deep reflexes on that side, a positive Babinski toe sign and allied reflexes. The sensory examination gave unsatisfactory results; there was, however, some hypalgesia over the right side of the body. The face was oily, and expressionless, and there was lack of associated movements of the right upper extremity. The right pupil was larger than the left; both reacted poorly to light and in accommodation and convergence. There were impairment in upward, downward and lateral gaze and nystagmoid jerks. Perioral tremor and right central facial weakness were present. There was incontinence of urine and, at times, of feces. The patient laughed and cried spontaneously, without being able to give a reason for it. On questioning, he said that he "did not know why he laughed or cried" and that he was not particularly "sad or happy" after such an episode. However, he expressed anxiety because of his physical and economic state. Although not mentally alert, he understood most of the questions. His memory was slightly deficient for remote events. During his stay in the hospital the temperature varied between normal and 101 F. The range in blood pressure was from 136 to 160 systolic and 86 to 98 diastolic.

Autopsy.—At the base of the brain a tumor, 5 cm. in diameter, lay between the left hippocampus and the left peduncle. The tumor invaded and compressed the following structures on the left: the hypothalamus, the medial and part of the lateral thalamic nuclei, part of globus pallidus, the corpus Luysi, the substantia nigra, the cerebral peduncle and the left mamillary body (fig. 7). In the region of the aqueduct, practically the entire left side of the mesencephalon was compressed (fig. 7).

Comment.—The invasion by the tumor of the structures named, the history of high fever and lethargy followed by right hemiplegia, with swelling of the right upper and lower extremities, extrapyramidal signs and pathologic laughing and crying, indicated that these symptoms were produced by the destruction and compression of the hypothalamus, thalamus, basal ganglia and cerebral peduncle. The pathologic laughing and crying may also have been caused by destruction of part of the mesencephalon. The simultaneous involvement of the mesencephalon does not exclude the possibility that the changes in the affective responses may have been caused by it.

CASE 33.—*Thrombosis of branches of the right middle and posterior cerebral and basilar arteries; involvement on the right of the putamen, internal capsule, medial and lateral thalamic nuclei and hypothalamus; pontile lesions; parkinsonism; pathologic laughing and crying.*

W. H., a man aged 64, had had fits of laughing and crying on any attempt to speak for three years.

Neurologic Examination.—There were fixed facies; a parkinsonian attitude, with rigidity and cogwheel phenomena; bilateral hyperreflexia, with signs of involvement of the right pyramidal tract; inability to protrude the tongue; explosive gales of laughter or fits of crying without provocation and on any attempt to

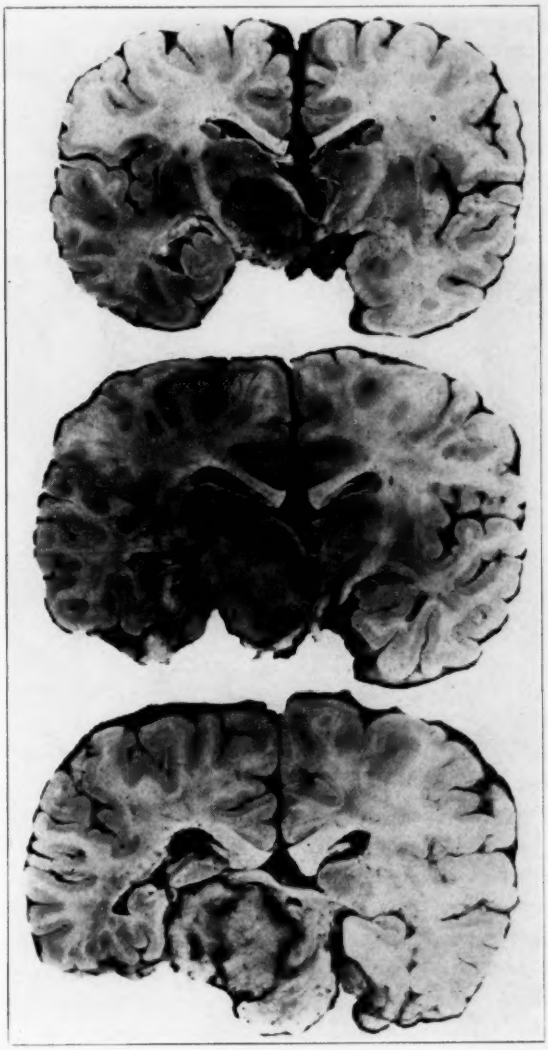

Fig. 7 (case 32).—Invasion and destruction by the tumor of the left portion of the hypothalamus, part of the medial and lateral thalamic nuclei and the globus pallidus, corpus Luysi, substantia nigra, cerebral peduncle and mesencephalon.

speak. Mental examination disclosed slight mental deterioration and poor memory for recent events.

Course.—On one occasion, after returning from the movies, which seemed to have upset him, he had episodes of joy and sorrow associated with bouts of

laughing or crying. When ill he became irritable. However, with any sign of improvement he was happy, wanted people about him and had more frequent bouts of laughter than of crying. Only once, while reading some depressing accounts in the newspapers, did he cry.

Autopsy.—There were areas of softening on the right side involving the putamen, the superior surface of the internal capsule, the medial and lateral nuclei of the thalamus and part of the hypothalamus (fig. 8). In the midbrain there were two small areas of softening involving the pontile fibers and part of the left substantia nigra (fig. 8).

Comment.—The spells of laughing and crying in this instance depended somewhat on the patient's manic personality. Pathologic were the degree of the reaction and the apparent absence or slightness of the

Fig. 8 (case 33).—Areas of softening of the right medial and lateral thalamic nuclei, hypothalamic nuclei and pontile fibers. Myelin sheath stain.

stimulus. There was needed always a stimulus, internal or external, and its affective tone conditioned the type and degree of the response. The degree of response seemed to be related to governing pathways from higher centers. The diffuse vascular lesions made it difficult to determine which of the regions involved were responsible for the affective responses. The lesions in the thalamus and hypothalamus, and possibly those in the pons, were most likely the cause of these phenomena.

CASE 34.—*Thrombosis of branches supplying the thalamus and hypothalamus on the right side; loss of pain and temperature sensibility over the left side of the body; querulousness; pathologic laughing and crying.*

R. G., a woman aged 50, had had previous episodes of cerebrovascular disease in 1928 and 1929, from which she recovered.

Neurologic Examination.—In 1929, there were bilateral athetosis; left flaccid hemiplegia, with signs of involvement of the pyramidal tracts; cerebellar signs on

the left; left external strabismus; loss of upward and lateral gaze; rotatory and vertical nystagmus; drooping of the right corner of the mouth; mimetic movements of the right side of the face, and myoclonic movements of the jaw, eye and tongue.

Course.—In February 1932 the patient became querulous and euphoric and showed frequent outbursts of forced laughing and crying. In addition to the previously noted neurologic signs, evidences of bilateral involvement of the pyramidal tracts and impairment of pain and temperature sensibility over the entire left side of the body were noted. Later, in September 1933, there developed marked memory defects, confusion, dysphagia and incontinence. She then became irrational and violent.

Autopsy.—The central nervous system in this case was cut serially. There were several areas of softening in the first and second frontal convolutions on the right. A larger area of softening destroyed the following structures on the right: practically all thalamic and hypothalamic nuclei, part of the internal capsule and the caudate nucleus (fig. 9 *A*). A fresh hemorrhage, on the left, destroyed the thalamic nuclei, the internal capsule, part of the corpus callosum and the caudate nucleus. There were other areas of softening in the tegmentum, one on the right destroying the nuclei of the sixth and seventh nerves, part of the corticopontile fibers and the central tegmental tract (fig. 9 *B*).

Comment.—Evaluation of the pathologic laughing and crying on the basis of the multiplicity of lesions in this instance is difficult. A careful survey of the events in the history, however, gives a clue. It was not until February 1932, when the patient showed loss of pain and temperature sensibility on the left side of the body, that she had outbursts of laughing and crying and querulousness. The lesions of the right thalamus (fig. 9 *A*) most likely were responsible for the sensory disturbances; those of the right thalamus or right side of the hypothalamus may have resulted in pathologic laughing and crying. The lesion in the right side of the brain stem, involving the nuclei of the sixth and seventh nerves and part of the pyramidal and the facio-respiratory fibers, may also have been the cause of the affective responses. This lesion must have existed prior to the thalamic lesion, for there was a previous history of involvement of the nucleus of the sixth nerve and rhythmic palatal myoclonus, without pathologic laughing and crying. The palatal myoclonus, as shown by one of us (Davison and associates [31]), was caused by the lesion of the right central tegmental tract.

CASE 35.—*Thrombosis of the left lenticulostriate artery; aphasia; hemiplegia; pathologic laughing and crying.*

L. D., a man aged 69, had right hemiplegia and aphasia in August 1933.

Neurologic Examiation.—There were slight expressive aphasia; right hemiplegia, with pyramidal tract signs; right facial paresis for volitional movements when at rest, but not during emotional response and pathologic laughing and crying.

31. Davison, C.; Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Larynx and Other Regions, Bull. Neurol. Inst. New York **4**:94, 1936.

Autopsy.—An area of softening on the left side had destroyed the upper fibers of the internal capsule, the superior aspect of the putamen and caudate nucleus and the globus pallidus and part of the external nucleus of the thalamus (fig. 10).

Comment.—The pathologic laughing and crying followed involvement of fibers originating in the striatum and thalamus, or those present in the internal capsule which have their origin in the cortex.

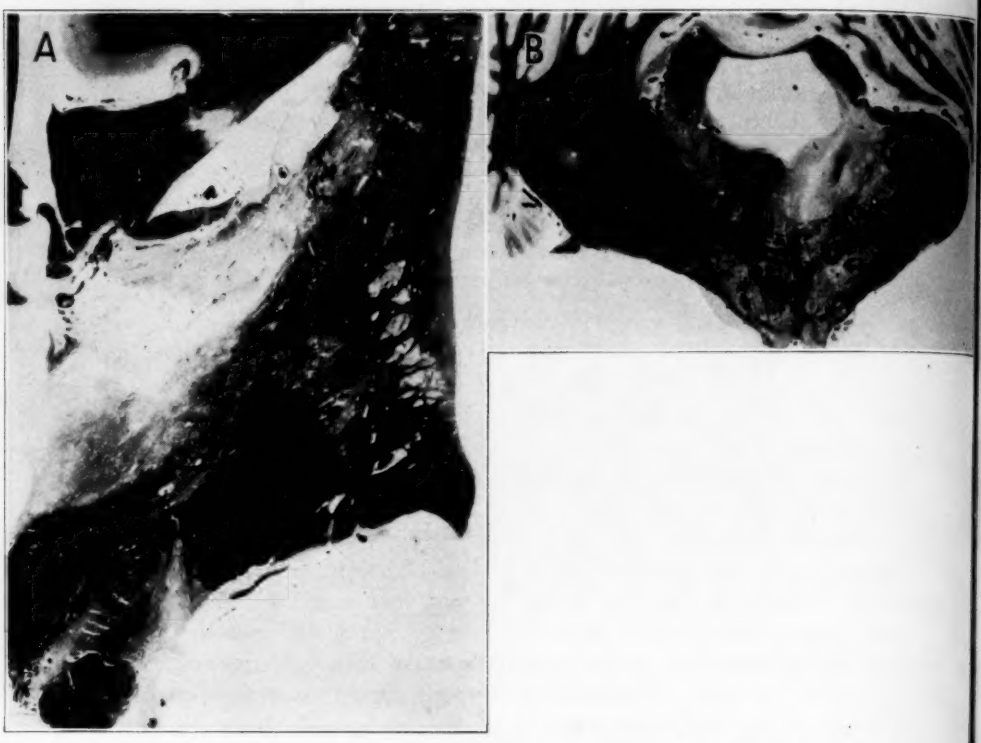

Fig. 9 (case 34).—*A,* area of destruction in the region of the thalamic and hypothalamic nuclei. The caudate nucleus and part of the capsular fibers are also involved. *B,* section of the brain stem through the nuclei of the sixth and seventh nerves, showing an area of softening on the right with destruction of the nuclei and fibers of the sixth and seventh nerves, the central tegmental tract, the posterior longitudinal bundle and some of the pyramidal tract fibers.

CASE 36.—*Occlusion of branches of the right middle and posterior cerebral arteries; thalamic lesion; pathologic crying.*

L. B., a woman aged 47, who had hypertension, experienced two cerebrovascular insults on the right side in 1931 and 1934, respectively. The last ictus was associated with frequent spontaneous crying spells and nervousness.

Neurologic Examination.—There were paralysis of the left side with pyramidal tract signs, including the face, and frequent, unmotivated outbursts of crying.

On Oct. 9, 1935, there appeared an acute confusional state, which was followed by intellectual deterioration.

Autopsy.—There were areas of softening on the right side, involving the putamen, pallidum, external capsule, corpus callosum and medial and lateral nuclei of the thalamus, and an area of softening in the left putamen and lateral thalamic nucleus.

Comment.—Definite conclusions cannot be drawn from the observations in this case, as the lesion involved not only the right thalamus but other structures. The possibility of injury of the cortical contingents

Fig. 10 (case 35).—Destruction of the superior aspect of the left internal capsule, caudate nucleus, putamen, pallidum and part of the external nucleus of the thalamus.

of the faciorespiratory mechanism as a result of involvement of the internal capsule must also be considered.

CASE 37.—*Parkinson syndrome; oculogyric crises, followed by pathologic laughing and crying.*

L. W., a woman aged 25, in 1927 had crying spells on the night of her engagement. One year later, during her first pregnancy, the spells recurred and were associated with malaise and irritability. After delivery, she had all the signs and symptoms of Parkinson's disease.

Neurologic Examination.—There was a typical parkinsonian picture, associated with blinking movements of the left eye when the patient was at rest, oculogyric and oculocephalogyric spasms and left supranuclear facial paresis on volitional movements. The oculogyric crises were associated with deviation of the eyes

upward, forward and downward, but never laterally. The patient also had spontaneous crying spells, which occurred either alone or after oculogyric crises. These lasted from a few minutes to six hours. She was able to recall having had a crying spell followed by a laughing spell, after oculogyric crises on two occasions. She was not sad when a crying spell started, but became so as it progressed. The crying at the beginning of an attack consisted of the usual respiratory and facial mechanisms, but at the end there were tears. When she tried to control the crying she made peculiar sobbing noises. The paresis of the left side of the face on spontaneous movements and mimetic responses varied with the degree of the patient's emotional tension; it was less marked when she was at ease. When her mood was one of laughter she gave way to her feelings. There was no change in the facial reaction. She was very irritable and easily upset and was extremely suspicious. During an attack her face and left arm and leg became rigid; her mouth became dry; her heart pounded; she perspired profusely and had frequency of urination. Some attacks were followed by narcolepsy or cataplexy or both. Either of these variations was usually followed by unmotivated crying spells.

Comment.—Although an autopsy was not performed in this case, the laughing and crying spells may be explained on the basis of involvement of the globus pallidus and substantia nigra, structures usually diseased in typical paralysis agitans. The tachycardia, profuse perspiration, frequency of urination and occasional attacks of narcolepsy and cataplexy are not unusual in the Parkinson syndrome and are possibly the result of lesions in the hypothalamus. It is well known that strong emotions may induce cataplexy. In this instance the sequence was reversed. The occasional association of oculogyric crises with crying and laughing spells, as in case 1, indicates an intimate connection of these two pathways.[32] In contrast to the affective responses in most cases, those in this instance were followed by the requisite mood. With the outbursts of laughing the patient became happy, and after her crying spells she was sad.

CASE 38.—*Dystonia musculorum deformans; outbursts of laughing and crying.*

M. G., a girl aged 13, had shown dystonic movements in 1934. Mentally she was retarded and tended to be seclusive.

Neurologic examination.—There were typical dystonic movements, with slight weakness of the right side of the face. The patient had many outbursts of crying, the crying being long drawn out and whining, with the jaws held wide apart. There were excessive grimacing and screwing up of the face. Outbursts of laughing and crying came spontaneously or occurred on the least provocation; at times they terminated in outbursts of screaming, which lasted for hours; throughout the screaming one could still determine whether the attack was initially one of laughing or crying.

Comment.—Although an autopsy was not done in this case, it is well known that in dystonia musculorum deformans, as demonstrated

32. Davison, C., and Goodhart, S. P.: Spasmodic Lateral Conjugate Deviation of the Eyes: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **25**:87 (Jan.) 1931.

by Goodhart and one of us (Davison),[33] the lesions are usually in the striatum, pallidum and dentate nuclei; occasional pathologic changes may be seen also in the cortex. This suggests that the basal ganglia send contingents to the pathways or centers concerned with this mechanism.

CASE 39.—*Progressive hepatolenticular degeneration; excessive smiling and outbursts of laughing.*

R. S., a woman aged 23, had typical hepatolenticular degeneration (Wilson's disease). Since the onset of the illness, the patient had noted that she smiled excessively and had unprovoked, spontaneous outbursts of laughing, which occurred only during the waking state, occasionally when alone but more often in the company of others. Even when the emotional situation warranted tears, laughter occurred.

Neurologic Examination.—There were tremors of the head and perioral region; action tremors of the upper extremities; ataxia; dyssynergia; typical "wing flapping" of the upper extremities; hypotonia and cogwheel phenomena of all extremities; dysarthric, scanning speech; inequality of the pupils, with the right greater than the left; pigmentation of the corneoscleral junction; constant grimacing, with the upper lip retracted above the gum; better mimetic than volitional responses; weak facial reflexes; outbursts of laughing, only during the waking state, and occasional outbursts of crying. Mental examination showed no disturbances, except for the effective responses and the mood. The patient expressed deep concern by saying: "Will I ever get well? Do you think you can help me? I feel I am getting sicker." While saying this she smiled almost constantly, occasionally with outbursts of toneless, expiratory laughter.

Comment.—The structures usually involved in this disorder are the striatum and the dentate nuclei. The striatum most likely sends fibers to, or is in intimate connection with, the centers or pathways which are concerned with this mechanism.

CASE 40.—*Spastic pseudosclerosis; spontaneous laughing and crying.*

J. R., a man aged 32, had weakness and unsteadiness of the left lower limb and the upper extremities, difficulty in speech and rigidity.

Neurologic Examination.—There were rigidity, drooling of saliva, spontaneous laughing and crying and ataxia of the upper limbs. Speech was dysarthric, explosive, scanning and at times monotonous. The interosseal muscles were atrophied, and there were generalized fibrillary twitchings, massive in character, of practically all muscle groups. There were increased tonus in all four limbs and cogwheel rigidity in the arms. The left foot had a striatal position. The deep reflexes were increased, and there was a Babinski sign bilaterally, with absence of abdominal reflexes. The face was oily, and there was right supranuclear facial paresis when at rest. The patient was deteriorated, apathetic, uncooperative and disoriented. Memory was poor for recent and remote events. He frequently went through the mimetic movements of laughing and crying; when asked why, he replied: "I can't help it." He felt happy when he laughed. When asked

33. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **29**:1108 (May) 1933.

to laugh and cry voluntarily he said he could not do it, and when he attempted to do so the results were imperfect.

Autopsy.—There were atrophy of the cerebral convolutions from the frontal to the parietal region; scantiness and destruction of the ganglion cells in the third, fifth and sixth layers; areas of devastation; proliferation of vessels; marked destruction of the giant pyramidal cells of Betz; demyelination of the pallidal segments; destruction of the nerve cells of the pallidum, corpus Luysi and hypothalamus, especially of the paraventricular nuclei; bilateral degeneration of the pyramidal tracts from the pons down, and degenerative changes in the anterior horn cells.[34]

Comment.—It is difficult to evaluate the pathologic laughing and crying in this instance, as pathologic changes were diffuse. The oily face and the associated involvement of the hypothalamic nuclei suggest that these structures may have played a role in the affective responses. The bilateral involvement of the pyramidal pathways throughout their course and of the faciorespiratory fibers and the basal ganglia is, however, the most likely cause of this phenomenon.

The following cases are abstracted only in brief.

CASE 41.—A. K., a man aged 58, had thrombosis of the lenticulostriate arteries and pontile branches of the basilar artery, which was verified at autopsy. There were bilateral pyramidal tract signs and uncontrollable, momentary outbursts of laughing and crying, at times amounting only to grunts.

CASE 42.—D. W., a girl aged 16, had typical hepatolenticular degeneration. Four other members of the family had Kayser-Fleischer rings. She seemed always in excessively good spirits, smiling much and given to impulsive outbursts of laughter, which shifted with ease to outbursts of crying and back again. Later her behavior became impulsive and self destructive.

CASE 43.—F. B., a man aged 38, had typical hepatolenticular degeneration, with a familial history. There were euphoria, facetiousness and excessive spontaneous laughing.

CASE 44.—F. K., a woman aged 24, had dystonia musculorum deformans. There were uncontrollable, explosive outbursts of laughter, lasting several minutes, without her feeling happy. Later normal laughing and crying became uncontrollable.

CASE 45.—I. C., a girl aged 8, had *athetose doublé*. There were fits of crying on the least provocation; the emotional responses were grossly exaggerated and prolonged, even to minimal stimuli. The patient had great difficulty in stopping the attacks of laughing or crying.

CASE 46.—G. L., a woman aged 42, had typical multiple sclerosis. She showed excessive smiling and easily motivated and uncontrollable laughing and crying, which she could control only temporarily. Her indomitable spirit was interpreted as euphoria.

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34. Davison, C.: Spastic Pseudosclerosis (Cortico-Pallido-Spinal Degeneration), Brain **55**:247, 1932.

LESIONS AT THE MESENCEPHALOMETENCEPHALIC LEVELS

There is sufficient experimental and clinical evidence that pathologic laughing and crying and allied affective responses can be produced by lesions at the mesencephalometencephalic levels. Woodworth and Sherrington,[35] and later Bazett and Penfield,[36] obtained slight "pseudo-affective" activity in decerebrate cats, such as biting, clawing and waving the tail. Keller,[37] by cutting through the middle and lower portions of the midbrain of decerebrate cats, elicited affective responses, such as spitting, growling, tail waving, pawing and sympathetic discharge. Magoun, Atlas, Ingersoll and Ranson [38] obtained coordinated facial and vocal activity (in response to unilateral and bilateral electrical stimulation of localized areas in the midbrain and pons) in the lightly anesthetized monkey and cat and in the acutely decerebrate cat. These areas included the central gray matter of the aqueduct and a bridge of tissue extending from this region through the dorsal part and into the lateral and ventral portions of the tegmental area. They concluded that these responses are "in part, at least, independent of afferent projections to the thalamus or cerebral cortex," and "that within the reactive area there is an efferent pathway or system for eliciting coordinated facial, vocal, and respiratory activity during the expression of emotion."

To our knowledge, clinicopathologic reports of cases of lesions at the mesencephalic level with these affective responses have not been published. Our case 51, that of a man suffering from multiple sclerosis, has been placed in this group only for illustrative purposes, as we realize that lesions elsewhere may have accounted for the pathologic laughing and crying. In our cases of lesions in the brain stem there is, however, conclusive evidence that involvement of the faciorespiratory pathway and nuclei and the descending hypothalamic tracts in this region may lead to emotional disturbances similar to those produced by lesions in the hypothalamus or other centers for emotional control. Spiller's case,[39] in which changes in the affective responses were caused by compression of the facial nerve or pons from an extracerebellar tumor, is additional evidence that the pons and medulla oblongata contain path-

35. Woodworth, R. S., and Sherrington, C. S.: A Pseudo-Affective Reflex and Its Spinal Path, J. Physiol. **31**:234, 1904.

36. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain **45**:185, 1922.

37. Keller, A. D.: Autonomic Discharges Elicited by Physiological Stimuli in Midbrain Preparations, Am. J. Physiol. **100**:576, 1927.

38. Magoun, H. W.; Atlas, D.; Ingersoll, E. H., and Ranson, S. W.: Associated Facial, Vocal and Respiratory Components of Emotional Expression: An Experimental Study, J. Neurol. & Psychopath. **143**:390, 1912.

39. Spiller, W. G.: Loss of Emotional Movement of the Face with Preservation of Slight Impairment of Voluntary Movement in Partial Paralysis of the Facial Nerve, Am. J. M. Sc. **143**:390, 1912.

ways, and possibly centers in the facial and ambiguus nuclei, for similar responses. Spiller used his case to illustrate the theory of the peripheral origin of pathologic laughing and crying as advocated by Bell[40] and Sanders.[41] Bell expressed the belief that differences in degree of involvement of the seventh nerve led to differences in function, whereas Sanders asserted that the peripheral portion of the seventh nerve contained separate sets of fibers for the affective and the volitional responses. This theory, however, has been discarded.

CASE 47.—*Partial occlusion of the right pontile branches of the basilar, right vertebral and anterior spinal arteries of the medulla oblongata; flaccid paralysis and sensory disturbances on the left side, associated with pathologic laughing and crying.*

R. L., a woman aged 54, had had paralysis of the left side in 1928 from which she recovered. In January 1933 she experienced a peculiar feeling of numbness on the left side of the body and could not use the left arm or leg. Shortly after this she noticed that she laughed or cried on the least provocation.

Neurologic Examination.—There were left flaccid hemiparesis, with pyramidal tract signs; complete loss of sensibility mediated by the posterior column on the left side of the body, with astereognosis and loss of two point discrimination; paralysis of the right external rectus muscle, with bilateral impairment of lateral conjugate deviation, more marked on the right; coarse nystagmus to the left and occasional nystagmus on upward gaze; complete right nuclear facial paralysis, and deviation of the tongue to the left, with questionable fibrillations. The patient laughed loudly or cried easily on the least provocation. The pathologic laughing or weeping did not depend on the emotional content of the occasion. Painful or humorous incidents were likely to produce either one or both emotional reactions. The patient showed great emotional lability.

Autopsy.—A thrombus partially occluded the right vertebral artery; it extended into the right anterior spinal artery, obstructing it completely. At its origin the basilar artery was also partially occluded. In the distribution of the right lenticulostriate artery, a small area of softening destroyed part of the caudate nucleus, internal capsule, putamen and globus pallidus. On the right side the brain stem was shrunken and atrophic, and an area of softening destroyed part of the right medial lemniscus and pyramid. Sections of the pons through the superior part of the fourth ventricle disclosed an area of demyelination of the lower part of the right pyramid and the right mesial fillet (fig. 11 *A*). Sections through the nuclei of the sixth and seventh nerves revealed an area of destruction involving the following structures on the right: the pyramid, the medial lemniscus, the posterior longitudinal bundle and the nuclei of the sixth and seventh nerves (fig. 11 *B*). Sections below this level showed, in addition to involvement of some of the preceding structures, implication of the corpus restiforme, the inferior olivary nucleus and the thalamo-olivary fibers.

Comment.—The involuntary laughing and crying in this instance followed the second vascular episode and were undoubtedly caused by

40. Bell, C.: The Nervous System of the Human Body, London, H. Renshaw, ed. 3, 1844, p. 256.

41. Sanders, W. R.: Facial Hemiplegia and Paralysis of the Facial Nerve, Lancet **2**:478, 1865.

the lesion in the region of the nucleus of the seventh nerve (fig. 11 *B*). Part of the faciorespiratory tract in this region was apparently involved. This case illustrates that lesions in the brain stem affecting the facial nucleus or the faciorespiratory tract may also induce pathologic laughing and crying. The nucleus of the seventh nerve is evidently in intimate relationship with the pathways and centers mediating these affective responses. Clinically, the involuntary laughing and weeping

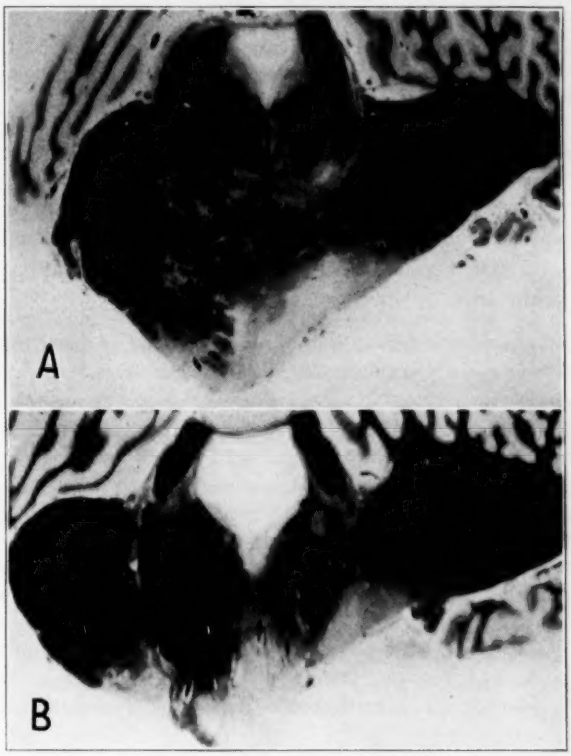

Fig. 11 (case 47).—*A*, section through the superior part of the fourth ventricle, showing demyelination of the lower part of the right pyramid and medial lemniscus. *B*, section of the brain stem at the level of the nuclei of the sixth and seventh nerves. Note the partial destruction of the nuclei of these nerves on the right and the demyelination of the right pyramid, medial lemniscus and posterior longitudinal bundle. Myelin sheath stain.

did not depend on the emotional content of the occasion. Humorous or sad incidents produced either one or both emotional responses.

CASE 48.—*Possible thrombosis of a branch of the basilar artery supplying the right facial nucleus and pyramid; left flaccid hemiplegia; peripheral facial paralysis; spontaneous laughing and crying.*

E. L., a man aged 57, had left flaccid hemiplegia, ataxia on the left side, right peripheral facial paresis and frequent bouts of laughing. The following is an account by the patient: "For months I would laugh very freely even when it wasn't funny; it just come on me. The laughing lasted for a few minutes, but I could stop it. When I needed to laugh or cry I could do so. Before I used to laugh freely; now I cry. Even when I see funny pictures I cry. I don't feel badly when it starts, but I am ashamed when it is over. It happens when I am alone and with people. I think my nerves are too weak. I really don't know why it happens." For about two years the patient showed moderate memory defects, a tendency to confabulate and occasional mild, transitory delusional trends.

Neurologic Examination.—There were paralysis on the left side with pyramidal tract signs; ataxia and intention tremor in the left upper extremity, and right nuclear facial paresis.

Comment.—Although necropsy was not performed, this case was selected because of the involvement of the pathways and centers for affective responses in the brain stem. The right peripheral facial palsy and left hemiplegia indicated a lesion in the brain stem, with possible involvement of the facial nucleus and the faciorespiratory pathways within the brain stem.

CASE 49.—*Amyotrophic lateral sclerosis; involvement of the pyramidal tracts only from the pons down; pathologic laughing and crying.*

S. L., a woman aged 44, gave a history of lisping and uncontrollable laughing and crying, followed by difficulty in swallowing, paresis and fibrillations of both upper and lower extremities.

Neurologic Examination.—There were bilateral pyramidal tract signs; atrophy and fibrillations of all muscle groups, and slight weakness of the right lower part of the face on voluntary and mimetic innervation. The patient was emotionally labile and was given to sudden outbursts of crying. Toward the end emotional instability was associated with irritability.

Autopsy.—There was disease of the anterior horn cells and some of the pontile nerve cells. Demyelination of the pyramids extended only from the pons to the lower parts of the spinal cord. The motor cortex, internal capsule and cerebral peduncles were normal. Some of the cells of the facial nuclei showed retrograde degeneration.

Comment.—The pathologic laughing and crying were probably due to the involvement of the faciorespiratory contingents of the cortico-pontonuclear tracts in the brain stem, since the pyramidal tracts above the level of the pons were normal. This case suggests that lesions of the pyramidal tracts limited to the brain stem may lead to pathologic laughing and crying. This pathway, which contains the supranuclear facial fibers, is probably the voluntary tract for the mediation of these affective impulses.

CASE 50.—*Amyotrophic lateral sclerosis; bilateral nuclear facial paresis; lesion apparently starting in the brain stem; unmotivated outbursts of laughing and crying.*

A. K., a woman aged 53, had had signs and symptoms of amyotrophic lateral sclerosis since 1929. In 1934 there appeared unmotivated outbursts of laughing

and crying. These occurred by day and night, even awakening the patient from sleep. They occurred when she was alone or with a group, when silent or in conversation and regardless of the relevancy of the emotional content. She did not feel happy before, during or after an outburst of laughing. She could be amused and laughed with appropriate affect. Crying was likewise uncontrollable. Although she felt badly because of it, her mood was not that of tears before or after the outbursts of crying.

Neurologic Examination.—There were signs and symptoms of amyotrophic lateral sclerosis; bilateral nuclear facial paresis in voluntary movement but almost none in emotional response, and involvement of the ninth, tenth, eleventh and twelfth motor cranial nerves. The spontaneous outbursts were mainly those of screaming, and as time went on she utilized these to dominate persons about her.

Comment.—Unusual in this case was the fact that the patient was awakened from sleep by the unmotivated outbursts of laughing and crying. Later, the spells were those of screaming rather than crying, and at times she wilfully screamed in order to dominate those about her. This is the only instance of our series in which the patient utilized this disorder for personal advantage.

CASE 51.—*Multiple sclerosis, with diffuse lesions involving the temporal lobes, mesencephalon, nucleus of the seventh nerve, striae acusticae and pyramidal pathways; uncontrollable outbursts of laughing.*

M. C., a man aged 28, complained that since 1917 he has had dizziness, diplopia, staggering gait, frequency of urination and numbness in the right upper and both lower extremities.

Neurologic Examination.—There were signs of disseminated lesions involving cerebellar, pyramidal and sensory pathways such as are usually seen in multiple sclerosis. There was also right facial paresis at rest and in volitional movements, with overreaction on emotional response. The facial expression was constantly that of laughter, and frequently there occurred unprovoked, uncontrollable emotional outbursts of laughing.

Course.—In 1930 the face became masklike, and the outbursts of laughing disappeared. There also developed at this time left volitional facial paresis and difficulty in swallowing. A psychiatric examination in 1934 indicated that the patient was well oriented; his memory and intellect were intact, and the attitude was one of subdued resignation. Euphoria was absent.

Autopsy.—Sclerotic plaques were present in the white matter of the right temporal lobe, the left hippocampus, the right internal capsule close to the end of the caudate nucleus, the white matter of both occipital lobes, the basal ganglia, tegmentum, cerebellum and brain stem. The larger plaque in the pons destroyed the greater part of the gray matter around the fourth ventricle. On the right there was involvement of the nucleus of the sixth nerve; on the left, of the nuclei of the sixth and seventh nerves (fig. 12 *A*), part of the central tegmental tract, the brachium pontis, the trapezoid body and the medial lemniscus (fig. 12 *A*). Two smaller plaques destroyed part of the pyramids. Sections below, through the nuclei of the eighth nerves disclosed a plaque in the cerebellar vermis, involving part of the left dentate nucleus and some of the nuclei in the roof of the cerebellum. Other plaques in the medulla oblongata destroyed, on the right, the striae acusticae, the vestibular nucleus, the nucleus ambiguus, part of the medial lemniscus, the spinothalamic tract and the other nuclear masses and fiber tracts in

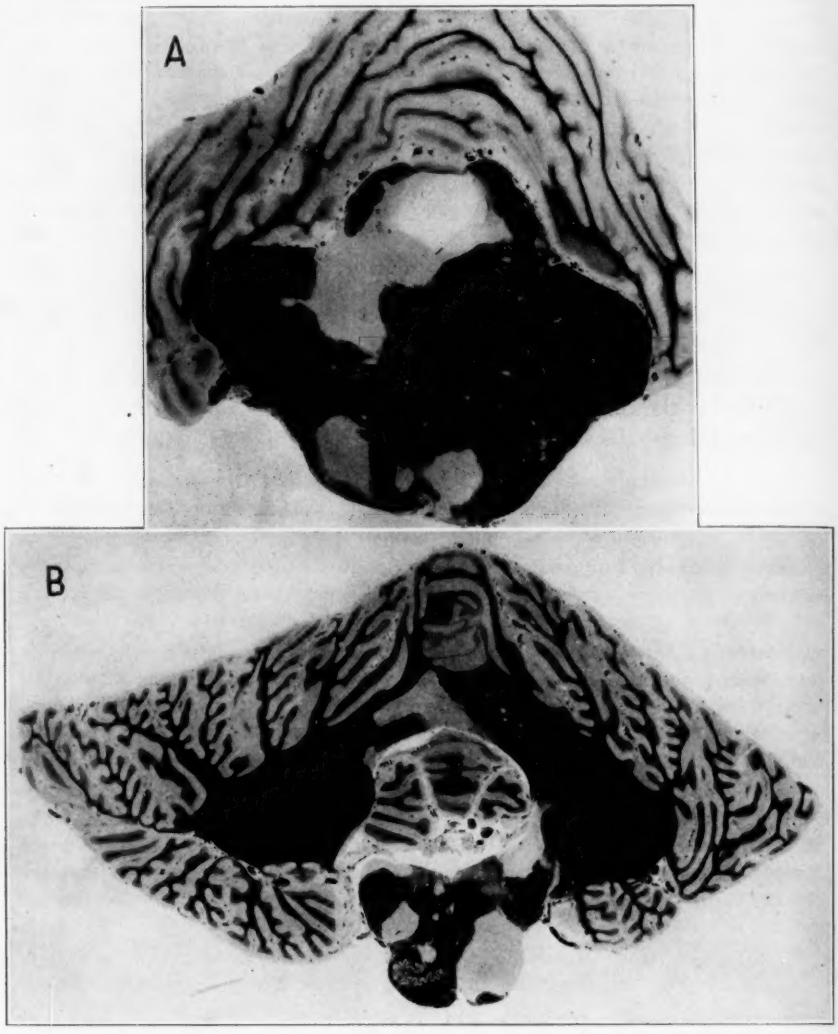

Fig. 12 (case 51).—*A*, several plaques in the pons, with a large plaque destroying the greater part of the gray matter around the fourth ventricle. On the right there is destruction of the nucleus of the sixth nerve; on the left, of the nuclei of the sixth and seventh nerves, the central tegmental tract, the brachium pontis, the trapezoid body and the medial lemniscus. Two smaller plaques destroy parts of the pyramids bilaterally. *B*, plaque destroying part of the cerebellar vermis and left dentate nucleus. Several plaques in the medulla oblongata destroy the striae acusticae, the vestibular nuclei, the nucleus ambiguus, the olivary nuclei, the corpus restiforme and the pyramid.

that region; on the left, the corpus restiforme, part of the lateral vestibular nuclei, the striae acusticae, the reticular substance, part of the olivocerebellar fibers and the dorsomedial surface of the left inferior olive (fig. 12 *B*).

Sections of the spinal cord revealed numerous plaques throughout all segments.

Comment.—Definite conclusions as to which of the structures involved were responsible for the pathologic laughing and uncontrollable emotional outbursts cannot be drawn in this case because of the multiplicity of lesions. The lesions in the temporal lobe, the tegmentum, the nucleus of the seventh nerve and the corticopontile fibers, regions which contain contingents for the mediation or inhibition of emotional reactions, may have been responsible for the pathologic laughter. Of interest in this case was the cessation of the emotional outbursts in 1930, when the face became masklike as a result of extrapyramidal involvement.

The following cases are abstracted in brief.

CASE 52.—B. A., a man aged 54, had typical amyotrophic lateral sclerosis, with degeneration of pyramidal pathways, starting in the brain stem. There were unmotivated outbursts of laughing and crying; later there was unprovoked, silly laughing, with rapid changes in mood and preservation of personality.

CASE 53.—G. O., a man aged 68, had typical amyotrophic lateral sclerosis, with degeneration of the pyramidal pathways, starting in the brain stem. There were euphoria and spontaneous outbursts of laughing and crying; later the patient became irritable.

ANATOMIC AND NEUROPHYSIOLOGIC CONSIDERATIONS

From an analysis of our clinicopathologic material, the cases reported in the literature and the results of animal experiments, it seems possible to reconstruct the centers and pathways regulating the affective responses, especially those for laughing and crying.

There is sufficient evidence that certain cortical areas, namely, the frontal, premotor, motor and sensory (as illustrated in our cases, in Mills' [42] case and in Bickel's experiment), may act as centers in the integrating mechanism for emotional expression and feeling. These impulses are mediated by voluntary and involuntary pathways. Voluntary action for the inhibition of the automatic movements, as suggested by Wilson, is controlled by the pyramidal tracts; involuntary action, by corticohypothalamic pathways (fig. 13). Involvement of part of the cerebral cortex undoubtedly removes its inhibitory control over the hypothalamus and other diencephalic nuclei, which are the main centers or

42. Mills, C. K.: Preliminary Note on a New Symptom Complex Due to Lesion of the Cerebellum and Cerebello-Rubro-Thalamic System, the Main Symptoms Being Ataxia of the Upper and Lower Extremities of One Side, and on the Other Side, Deafness, Paralysis of Emotional Expression in the Face, and Loss of the Senses of Pain, Heat and Cold over the Entire Half of the Body, J. Nerv. & Ment. Dis. **39**:73, 1912.

stations for the release of affective responses (fig. 13). The intimate relationship between the cortex and the hypothalamus is best illustrated by the series of cases of lesions at the corticodiencephalic levels.

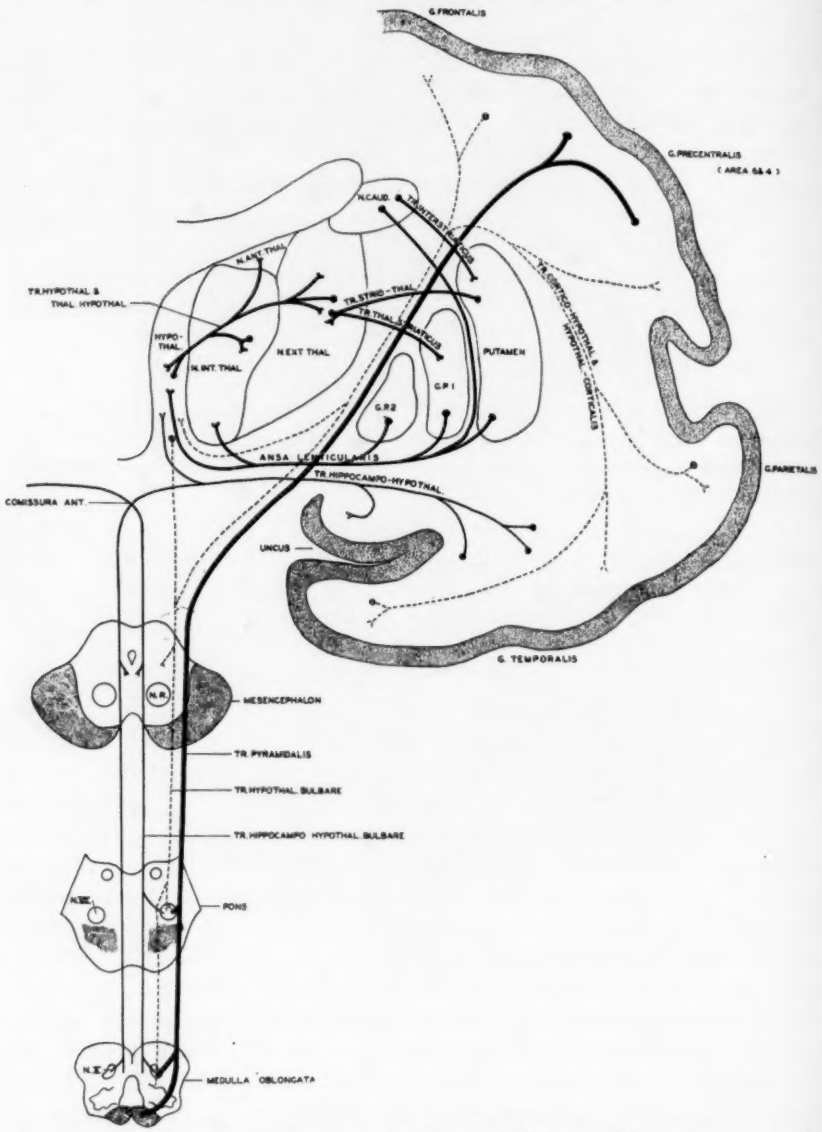

Fig. 13.—Schematic representation of the hypothalamus and its connections with other centers involved in the mechanism of pathologic laughing and crying.

The importance of the hypothalamus and other diencephalic structures is illustrated by clinicopathologic reports (Brissaud, Giannuli, Weisenburg and Guilfoyle, Dupré and Devaux, de Burzio, Alpers and

others) and by experiments performed on animals and on human subjects (Bard, Fulton and Ingraham and Foerster). Bard indicated that strong emotions, such as rage, are subcortical in origin and are most likely dependent on the caudal half of the hypothalamus. In a series of 36 successful acute experiments, sham rage occurred regularly after ablation of the corpora striata and the rostral half of the diencephalon; it appeared "in typical form after still more truncations of the brain-stem. Sham rage of maximal intensity occurred when there remained above the midbrain only a thin caudal segment of the diencephalon." Bard also obtained loud growling, hissing and biting in decorticate cats when they were stimulated in various ways. He expressed the belief that the remaining small fragments of some of the thalamic nuclei were of no functional significance and that the "full capacity of the affective expressions depends upon an intact hypothalamus." Head and Holmes [43] and others [44] demonstrated that the thalamus is under cortical inhibitory influence and is possibly a center for affective experiences. They claimed that a lesion of the corticothalamic fibers releases cortical control, thereby inducing excessive affective responses to certain stimuli.

As already stated, Bard expressed doubt concerning the existence of pathways and stimuli of cortical origin because cases of emotional paralysis following a cortical lesion have not been recorded. He adduced as further proof of this theory the presence of emotional paralysis with retention of volitional control because, according to him, the lesions provocative of this affect are invariably subcortical. Although this kind of response, as shown by other observers, is caused by lesions of the thalamus or the ventral part of the diencephalon, our cases and those reported by Friedman and Schick [45] indicate that cortical lesions may also be responsible for this phenomenon. Bard agreed with Pavlov [46] that by means of the cortex the inborn, stereotyped emotional reactions become, as a result of experience, conditional responses and that the production of emotional responses by conditioned stimuli are caused by release from cortical inhibition. Our cases of cortical lesions indicate that the cortex may be the seat of origin of such impulses. Bard expressed agreement, however, with Hughlings Jackson that the decortication in his experiments acted as a "release" of the subcortical rage mechanism from the inhibitory influence of the cortex. The secondary involvement of the thalamic nuclei, striatum and pallidum in many of the clinicopathologic cases and the edema of these structures in the

43. Head, H., and Holmes, G.: Sensory Disturbances from Cerebral Lesions, Brain **34**:102, 1911.

44. Head, H., and others: Studies in Neurology, New York, Oxford University Press, 1920, vol. 2, p. 620.

45. Friedman, E. D., and Schick, W.: Personal communication to the authors.

46. Pavlov, I. P.: Conditioned Reflexes, New York, Oxford University Press, 1927.

experimental animals suggest that these areas may also act as centers for the appearance of these affective responses or that, by means of pathways, they are in intimate connection with the hypothalamus (fig. 13). Interruption of these pathways on their way to the hypothalamus or of the descending hypothalamic pathways may lead to the production of the same mechanism. The induction by Foerster of manic-like reactions by irritation of the hypothalamus in the human subject in the presence of an intact cerebral cortex is additional evidence of the significance of the hypothalamus as a main center for affective responses.

The importance of lesions of the mesencephalon and metencephalon in the production of pathologic laughing and crying and allied affective responses is well illustrated by a group of our cases, the few cases recorded in the literature (Wilson; Spiller) and the experimental work on animals (Woodworth and Sherrington; Bazett and Penfield; Keller; Magoun, Atlas, Ingersoll and Ranson). Magoun and his associates concluded that the coordinated facial and vocal activity in response to electrical stimulation of localized areas in the midbrain and pons is "in part, at least, independent of afferent projections to the thalamus or cerebral cortex" and that within the reactive area there is an efferent pathway or system for eliciting coordinated facial, vocal and respiratory activity during the expression of emotion. The association of automatic facial movements with the involuntary respiratory mechanism was shown experimentally by Graham Brown.[47] After transecting the mesencephalon, he stimulated a small area between the internal boundary of the red nucleus and the midlongitudinal dorsoventral plane of the neuraxis. This produced deep and steady respiration as well as rapid and shallow breathing, resulting in sounds somewhat similar to that of laughing. Stimulation of an area at the extreme caudal end of the thalamus caused vigorous and hollow breathing, while excitation of the ventral part of this area produced slowing of respiration. The results of the experimental work of Magoun and his associates and of Brown are in agreement with those of Wilson's illuminating clinical studies. Wilson suggested that both the facial and the respiratory mechanism participate in the act of laughing and weeping, both physiologically and pathologically. The association of the facial and the respiratory musculature in emotional expression is clearly evident in normal and abnormal breathing, in speaking, in sneezing, coughing and yawning and in laughing and weeping. As already indicated, Wilson postulated a center linking the muscles of the seventh nerve with the nucleus ambiguus (tenth) and the nuclei of the phrenic nerve. This faciorespiratory mechanism has a supranuclear voluntary control for inhibition of auto-

47. Brown, T. G.: Note on the Physiology of the Basal Ganglia and Midbrain of the Anthropoid Ape, Especially in Reference to the Act of Laughter, J. Physiol. **49**:195, 1915.

matic movements and an involuntary control for the release of emotional expression. He based this opinion on Spencer's experimental work in 1894. Spencer demonstrated four pathways from the cerebral cortex to the respiratory mechanism, the involuntary and the voluntary pathways. The involuntary pathways consist of the following: 1. A slowing and arresting pathway, arising just outside the olfactory tract, where it joins the temporoparietal lobe. This tract enters the olfactory limb of the anterior commissure, where it decussates. Then it continues backward beside the infundibulum, past the red nucleus, below and external to the aqueduct in the plane of exit of the third nerve, and into the medulla oblongata. 2. An accelerating pathway, arising from the sensorimotor cortex and continuing through the lenticular nucleus, where it borders on the outer and ventral portion of the internal capsule, runs first external and then ventral to the motor portion of the internal capsule and reaches the tegmentum. The lines from the two sides meet in the interpeduncular gray matter, at the level of and just behind the plane of the third nerves. 3. A less well defined pathway, producing overinspiratory clonus ("snuffing movements"), arises at the junction of the olfactory bulb and tract and continues into the uncinate convolution. Followed to the uncus, it passes behind the optic tract to the crus; then passing obliquely beneath the crusta, it converges in intimate relation with the middle line of the upper border of the pons. The voluntary pathway, producing overinspiratory tonus, forms part of the pyramidal tract. Part of the involuntary pathways possibly are made up of fibers coming from the hypothalamus, described later by Beattie, Brow and Long,[48] which descend in the medulla oblongata and spinal cord.

Wilson expressed the belief that there are corticofugal pathways to the faciorespiratory centers in the pons and medulla oblongata, independent of the voluntary pyramidal tract to the same nuclei. Their exact course has not yet been determined. On excitation they interfere with the normal rhythmic activity of the respiratory center. According to Wilson, these are possibly the routes taken by emotional impulses in modifying the faciorespiratory mechanism in the acts of laughing and weeping.

On the basis of the foregoing observations, an attempt at a schematic reconstruction of the various centers and pathways appears advisable. The main center of the affective responses is the hypothalamus, which sends and receives fibers to and from various parts of the cortex by means of the hypothalamocortical and corticohypothalamic pathways (fig. 13). In turn, the hypothalamus is also in intimate connection with

48. Beattie, J.; Brow, G. R., and Long, C. N. H.: The Higher Connections of the Sympathetic Nervous System as Studied by Experimental Lesions of the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **9**:295, 1930.

the thalamus, striatum, pallidum, midbrain, pons and facial and ambiguus nuclei (fig. 13). Cases of extrapyramidal disease illustrate the role of the striatum and pallidum in the release of these affective responses. This undoubtedly is produced by direct interference in the pathways connecting the extrapyramidal structures with the hypothalamus or by means of the thalamic connection. Some of the experimental and clinicopathologic reports of thalamic lesions indicate the importance of the diencephalon in this mechanism. The function of the midbrain and pons was illustrated by Magoun and his co-workers in the production of affective responses when these structures were stimulated electrically. Another possible important pathway is the slowing and arresting pathway postulated by Spencer, which arises somewhere in the temporoparietal lobe, just outside the olfactory tract, enters the olfactory limb of the anterior commissure (fig. 13), where it decussates, and continues beside the infundibulum, external to the aqueduct, and into the medulla oblongata, where it may send or receive fibers from the facial and ambiguus nuclei (fig. 13). This pathway is possibly also in intimate connection with the hypothalamus. Lastly, the voluntary pathway for these affective responses is situated essentially in the pyramidal tract, which is also in intimate relation with the facial and ambiguus nuclei (fig. 13). The importance of this pathway for the release of affective responses is well illustrated by the patient with a motor cortical lesion (case 2) and the cases of amyotrophic lateral sclerosis (upper and lower motor neuron disease). That pathologic laughing and crying can take place in association with lesions of the pyramidal pathways in the pons is also illustrated by the cases of amyotrophic lateral sclerosis in which the degeneration of these tracts started in the pons and medulla oblongata.

PSYCHOLOGIC CONSIDERATIONS

A psychologic analysis of these emotional outbursts is indicated. As the theory of emotions was first described by James [49] and James and Lange,[50] a brief discussion and criticism in the light of present neurophysiology will be given.

According to this theory, consciousness of the bodily functions is the essential element in emotional consciousness. According to Lange, stimulation of the vasomotor center produces vascular changes, which in turn induce changes in bodily and mental functions and therefore in emotions, such as anger, fear, joy and sorrow. James asserted that stimulation of the vasomotor center is not all important, but expressed the opinion that "particular perceptions produce widespread bodily effects by a sort of immediate physical influence, antecedent to the

49. James, W.: The Physical Basis of Emotions, Psychol. Rev. **1**:516, 1894.

50. James, W., and Lange, G. C.: The Emotions, Baltimore, Williams & Wilkins Company, 1922, p. 135.

arousal of an emotion or an emotional idea." An emotion, therefore, in James's opinion, is unable to exist without the consciousness of all the feelings of its characteristic bodily symptoms. According to these combined theories, emotional stimuli induce a motor or efferent discharge to the effector organs, from which afferent impulses surge back, activating the intellectual perceptions which underlie emotional feeling.

Cannon and his co-workers,[51] by removing all visceral sensations in the sympathectomized cat, succeeded in eliciting emotional reactions such as "hissing, growling, retraction of the ears, showing of the teeth, lifting of the paw to strike—except erection of the hairs." They thus disproved the James-Lange theory that emotions are in any way dependent on visceral changes. According to Cannon and Britton,[52] all these states activate the entire sympathetic system and in turn affect the viscera, which are under sympathicoadrenal influence. Cannon, Querido, Britton and Bright [53] have shown further that with shivering from cold there occur visceral changes, but no emotional responses, similar to those in fright—a further refutation of the James-Lange theory. Additional evidence against the James-Lange theory is the case cited by Dana [54] of a high cervical transection, as a result of which he concluded that stimuli from the entire sympathetic and somatic systems were eliminated. In spite of this, the emotional feelings in this and similar cases were not changed. Dana's cases further substantiate the validity of the animal experiments for the resultant phenomena were the same whether consciousness was apparently disturbed or not.

Dana [54] and, later, Cannon [55] suggested that emotion is dependent on the functions of the cerebral cortex and diencephalon; the cerebral cortex is the site of emotional consciousness. According to Cannon, the diencephalon discharges impulses upward to the cortex by means of the hypothalamicocortical pathways, thus evoking emotional consciousness. The efferent impulses discharging from the diencephalon downward produce the emotional response after having reached the cortex

51. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: The Dispensability of the Sympathetic Division of the Autonomic Nervous System, Boston M. & S. J. **197**:514, 1927. Cannon, W. B.; Newton, H. F.; Bright, E. M.; Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, Am. J. Physiol. **89**:84, 1928.

52. Cannon, W. B., and Britton, S. W.: Conditions of Activity in Endocrine Glands: Pseudoaffective Medulliadrenal Secretion, Am. J. Physiol. **72**:283, 1925.

53. Cannon, W. B.; Querido, A.; Britton, S. W., and Bright, E. M.: The Role of Adrenal Secretion in the Chemical Control of Body Temperature, Am. J. Physiol. **79**:466, 1927.

54. Dana, C. L.: The Anatomic Seat of the Emotions: A Discussion of the James-Lange Theory, Arch. Neurol. & Psychiat. **6**:634, 1921.

55. Cannon, W. B.: The James-Lange Theory of Emotion: A Critical Examination and an Alternative Theory, Am. J. Psychol. **39**:106, 1927; Again the James-Lange and the Thalamic Theories of Emotion, Psychol. Rev. **38**:281, 1931.

and being affected by it. When the impulses reach the cortex there is a change from the "object simply apprehended" to the "object emotionally felt." While James attributed the "object emotionally felt" to the "widespread bodily effects," Cannon expressed the belief that "the peculiar quality of the emotion is added to simple sensation when thalamic processes are aroused" or when the cortex is affected by a diencephalic discharge. This theory, according to Bard, readily explains "the cases of unilateral release of the thalamus from cortical control with accompanying ipsilateral intensification of emotional tone." These cases, according to Cannon, further disprove the complete validity of the James-Lange theory, for the "viscera cannot function by halves, these patients do not engage in one-sided expression of their emotion, and the impulses sent back to the disturbed periphery are bilateral; the unsymmetrical feeling is due to the organ which is functioning unsymmetrically—the diencephalon." Emotional feeling in some cases of aphasia can exist without emotional expression because of the destruction of the efferent pathways. According to Cannon's theory, feeling must be central in origin, and it is transmitted by afferent impulses from an intact thalamus. In cases of extensive lesions of the diencephalon, as in those of Fulton and Bailey,[56] the expression and the feeling disappear together. The foregoing arguments based on multiple possibilities indicate rather that the diencephalon is not solely accountable for these emotions, but is only part of an integrating system.

The diencephalic theory of Cannon and Bard, while it explains the affective responses as a result of lesions in the diencephalon or below it, as indicated by Magoun and his co-workers, does not adequately help one to understand the cases in which there are pure cortical lesions. The several instances in our series of selective lesions of the cortex—frontal, motor or sensory—show that the cortex when diseased may lead to the production of these affective responses; in other words, "the object simply apprehended" can also be "emotionally felt." It appears that the involvement of the sensory cortex in case 1 would disprove the foregoing theory. This, however, is not the case, for the sensory area, as well as other parts of the cortex, sends and receives fibers from the diencephalic region. Irritation or disease of these fibers anywhere in their course may lead, as in our instances, to the affective responses which may be apprehended and felt. At times the affective responses may be apprehended, but apparently without the requisite feeling tone.

That such pathways are present not only in the cortex and diencephalon but also in the mesencephalon and brain stem is proved by our cases and those of other investigators. In the brain stem, undoubt-

56. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle, J. Nerv. & Ment. Dis. **69**:1, 145 and 261, 1929.

edly, efferent and afferent impulses from the diencephalon were not cut off completely, and therefore the complete influence of the diencephalic centers could not have been eliminated.

PSYCHODYNAMICS

The obstruction of instinctive drives results in tensions, which ultimately find expression in emotions. The form and feeling tone of these emotions, as described by the patient, may apparently be adequate or exaggerated or disjointed and inappropriate. These variations are present in pathologic laughing and crying. Limited motor inhibition and control of feeling from higher centers may lead to exaggeration of these affective responses. In the normal state and in the less severe forms of neurosis extremes of feeling and expression are not as frequently in evidence. In the more acute and severe forms of neurosis and in the psychoses the laughing and crying may closely simulate the pathologic laughing and crying described here. Disease of the centers and pathways controlling these emotions may lead to responses the reverse of the expected.

Laughing and crying are so intimately connected that fragments of the feeling tone and expression of both may be present at the same time. This is understandable, since one knows of "gallows humor" and "joyful weeping." A patient laughed uproariously and uncontrollably the moment any one approached him. The upper part of his face expressed tearful sadness; the lower laughter, while his true mood was one of anguish. One patient's mood appeared euphoric, but he said he felt sad. He smiled when he said he was concerned about his illness. At no time before, during or after laughing did he feel happy. In a few instances the patients seemed entirely indifferent and apparently unaffected by the laughing or weeping because they did not regard these emotional experiences as a part of themselves. This apparently is in contradiction to Wilson's belief that the emotional display is a genuine manifestation of feeling. Some patients were only slightly annoyed; others were confused and bewildered by these attacks, and still others accepted the outbursts with resignation. Many tried to attribute the spells, particularly those of crying, to the fact that they were nervous or sad, while most patients admitted that they did not know the meaning of the attacks. In the case of 1 patient, during states of emotional tension the crying spells became uncontrollable. Two years later there developed a complete picture of postencephalitic parkinsonism, with spontaneous and uncontrollable spells of laughing and crying, possibly indicating that the early crying spells were a larval form of the later attacks. Such emotional expressions are apparently unexplainable only because the psychogenic mechanisms which may have stimulated these

responses are not readily available to consciousness. This is brought about probably because of disease of the centers and pathways concerned with this mechanism. The patient's inability to explain these affective responses does not mean that they cannot be understood.

Since feeling and expression are the result of phylogenetic and ontogenetic experiences, it is evident that some emotions function automatically, without reaching consciousness. Stimuli from within or without may set off feelings and expressions which are apparently not understood. This problem is best understood if one includes under the term "the unconscious" all those ancient and recent emotional experiences and all stimuli not immediately available to consciousness. When the stimuli causing these responses are evident it seems that the unconscious need not be considered. One knows, however, that reactions which these stimuli set off occur only in terms of experience. These reactions, however, consisting of feeling tones or emotional expression or both, may result from similar unconscious stimuli affecting the unconscious.

Figure 14 is an attempt to illustrate all the possible combinations that may occur as the result of a stimulus setting off a progressive phenomenon, which becomes exaggerated or altered by reverberations from the unconscious. This diagram illustrates that all stimuli, conscious or unconscious, activate the unconscious to produce feelings (F_1) or expressions (E_1) of laughing (L_1) or crying (C_1). When either type of feeling (L_1, C_1) reverberates to the unconscious, it adds the particular expression (E_2, L_2, C_2) stimulating it. Conversely, when either type of expression (E_1, L_1, C_1) returns to the unconscious, it adds the particular feeling (F_2, L_2, C_2) stimulating it. The number of clearcut possibilities is indicated on the diagram, but the degrees of differences within this group are myriad. Hence, "mixed feelings" and "mixed expressions" are understandable entities.

The preceding considerations are based on an analysis of our material. One patient often awakened from sleep with an uncontrollable crying spell, and another, laughing, crying or screaming. In these cases the unconscious emotional tensions operating while the patients were asleep were most likely the stimuli setting off these emotional expressions. It was not possible to link these occurrences to nightmares, unpleasant dreams or any other kind of dreams. The mood in some of these instances was one of sadness, but only because the patients felt so tortured that even during sleep they could not be free of these afflictions. Another patient when torpid and drowsy had spontaneous crying spells; yet when awakened he was euphoric and did not realize the seriousness of his illness.

This patient showed another interesting phenomenon. The spontaneous crying spells present before the operation disappeared after

removal of the tumor, but the uncontrollable outbursts of crying persisted. In time, possibly because of recession of edema and radiotherapy, this patient was successful in preventing any further attacks, although sniffling and tears were still present. One patient had spells of laughing and crying but could not laugh or cry voluntarily. Another had both types of attacks but could also voluntarily give vent to his feelings. In 1 case uncontrollable crying spells were sudden in their onset and termination. In a case of progressive hepatolenticular degeneration the attack shifted with extreme ease from outbursts of laughing

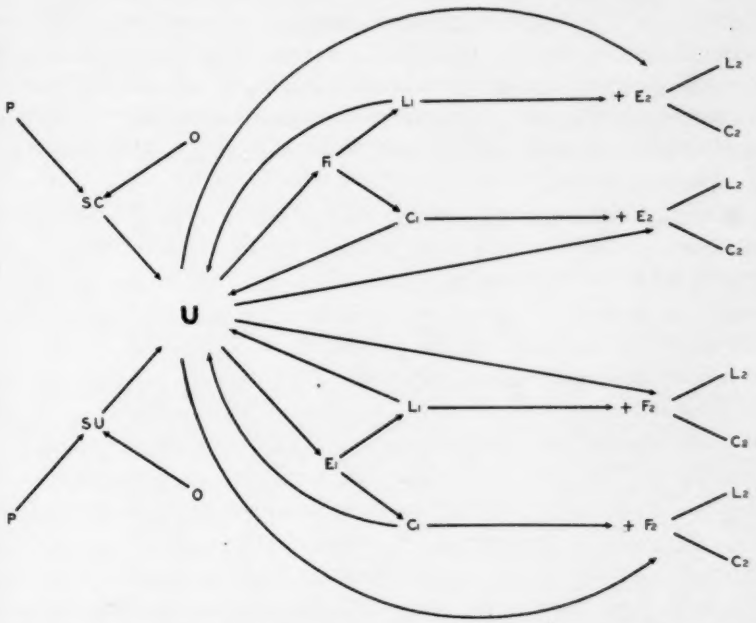

Fig. 14.—Schematic representation of combinations that may occur as the result of a stimulus setting off a progressive phenomenon. In the diagram, *U* indicates the unconscious; *P*, psychic; *O*, organic; *SC*, conscious stimulus, and *SU*, unconscious stimulus. All of these stimuli, conscious or unconscious, activate the unconscious to produce feelings (F_1) or expressions (E_1) of laughing (L_1) or crying (C_1). When either type of feeling (L_1, C_1) reverberates to the unconscious, it adds the particular expression (E_2, L_1, C_1) stimulating it. Conversely, when either type of expression (E_1, L_1, C_1) returns to the unconscious, it adds the particular feeling (F_2, L_2, C_2) stimulating it.

with euphoria to crying with irritability. In another, the same thing occurred, but from the patient's facial expression one could not tell whether he was laughing or crying, nor was he able to state how he felt or what he was doing; this patient was mentally clear. In a case of *athetose doublé* spontaneous attacks of laughing and crying did not

occur, but minimal stimuli produced these uncontrollable outbursts, which were of extreme violence. One patient could temporarily stop the laughing spell, while another could carry on a conversation in the midst of an attack. Another had attacks of crying whenever he tried to talk, and even the crying was toneless. Some patients with motor aphasia had uncontrollable laughing and crying spells, and some continued to have these attacks when the aphasia disappeared. One patient with slight aphasia had, on the least provocation, outbursts of laughter and weeping and temper tantrums without basis. The laughing and crying disappeared when the aphasia became complete and were replaced by screaming. Crying spells in some instances were noiseless because of volitional control, but the associated respiratory and facial phenomena were still present. One patient had spells during which she went through the mimetic movements of laughing and crying, but without the respiratory changes. Another patient had forced laughing, and at times only an expiratory grunt.

When a pathologic expression of laughing or crying is sufficiently prolonged or intense it may evoke a happy or a sad mood. One patient early in his illness had uncontrollable laughing spells which always terminated in a mood of happiness, while later he had only crying spells, after which he was sad. In the patients with both types of outbursts, the predominant reaction was generally dependent on the patient's past and present attitude toward life. In general, the frequency of crying was much greater than that of laughing. This was not surprising. At times the crying was accompanied by outbursts of irritability. The unhappiness caused by the affliction discounts even an optimistic attitude, except in cases of diminution or absence of insight or of euphoria (multiple sclerosis, tumor of the brain or true hypomania). Sadness may be present with either type of attack because of the patient's inability to control the outburst and because of the forced limitation in social contact. The patients fear appearing ridiculous or being regarded as insane. This is best illustrated by the following cases: In 1 case an attempt to speak set off an attack of laughing; in another, an attack of crying. As a result, the vocal expressions were limited. The approach or presence of friends in some instances set off gales of laughter or violent weeping. Some patients were plagued with these unpleasant outbursts, even when alone. In several cases the crying became modified to whining, or even to screaming; with the former there was frequently petulance; with the latter, irritability or great anguish. Cataplexy may also occur after a violent outburst of laughing or crying (Wilson's case and our case 37 of cataplexy and narcolepsy). At no time is consciousness disturbed during attacks.

SUMMARY AND CONCLUSIONS

From an analysis of the clinicopathologic material presented, the cases reported in the literature and animal experiments, it is possible to reconstruct the centers and pathways regulating these affective responses.

The cases of cortical lesions indicate that certain cortical areas, namely, the frontal, premotor, motor, parietal, temporal and hippocampal, may act as centers for integration of these affective responses. These impulses are mediated by pathways which are in intimate connection with the hypothalamus. This is illustrated best by the series of cases in which there were lesions at the corticodiencephalic level. The hypothalamus or some of the other diencephalic nuclei, which are under cortical inhibitory influence, are the main centers or stations for the release of affective responses. A lesion of the corticohypothalamic tract removes cortical control, thereby inducing excessive affective responses. The secondary involvement of the thalamic nuclei, striatum and pallidum in many of the clinicopathologic cases and the edema of these structures in the experimental animal suggest that these areas may also act as centers for the production of these affective responses and that, by means of pathways, they are in intimate association with the hypothalamus.

The group of cases of selective lesions of the mesencephalon and metencephalon and the animal experiments indicate that there are pathways, and possibly independent centers, in these regions for the production of laughing and crying. Some of these pathways are in intimate connection with the hypothalamus and the faciorespiratory nuclei.

The various psychologic theories for the emotions are discussed. It is emphasized that the pathways and centers aforementioned, particularly those of the faciorespiratory mechanism, are important for the expression of the emotions and that the stimuli setting them off may be cortical or subcortical or both. No single structure is all important, and all must be integrated for control of feeling and expression.

A psychodynamic study of pathologic laughing and crying indicates that a number of variations may occur. These emotions apparently may be adequate or exaggerated in their form or feeling tone, as described by the patient. The responses may also be actually or seemingly disjointed and inappropriate. The spontaneous laughing and crying in the psychoses and neuroses are not included in this study. Although these will have to be explained on purely psychologic grounds, the seat of their origin and their transmission most likely depend on the centers and pathways described.

TREATMENT OF SCHIZOPHRENIA WITH GLANDULAR EXTRACTS

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I have previously proved by means of experiments that schizophrenia is regularly accompanied by a disturbance in metabolic energy. The results, already published,[1] were based on the investigation of 277 cases, in most of which more than one examination was made. The disturbance in the rate of oxygen consumption shows itself in alteration not only of the basal metabolic rate, a factor I wish particularly to stress, but also—and this is of great importance for further research—of the specific dynamic action of protein.

By the specific dynamic action of protein I mean, in accordance with Rubner's investigations, the rise in the consumption of oxygen simultaneously with the increase in the production of carbon dioxide after the ingestion of protein. The highest point is reached one or one and one-half hours after ingestion. In normal persons, when they are given 200 Gm. of meat the specific dynamic action of protein rises to at least 18 per cent above the basal metabolic rate, as Kestner, Liebeschütz-Plaut and Schadow [2] have also proved.

The most important results of the former investigations may be summarized as follows:

In the early stages of schizophrenia the specific dynamic action of protein falls first; afterward the basal metabolic rate sinks gradually, and the specific dynamic action rises. As the disease advances the basal metabolic rate remains below normal, while in most cases the specific dynamic action reaches a normal level again. In a few cases the basal metabolic rate does not fall; the specific dynamic action alone is decreased.

The basal metabolic rate or the specific dynamic action of protein or both remain below normal as long as the illness persists.

When the psychotic symptoms disappear, the oxygen consumption does not become normal immediately, but returns to normal after a short time.

In the event of reappearance of the disease, the alteration in oxygen consumption is repeated.

When only an imperfect mental recovery has been effected, the disturbance in the oxygen consumption remains, usually as a decrease in the basal metabolic rate and more rarely as a reduction in the specific dynamic action of protein or as both.

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1. Fischer, S.: Klin. Wchnschr. **6**:1987, 1927; Arch. f. Psychiat. **83**:205, 1928; Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:109, 1933.

2. Kestner, O.; Liebeschütz-Plaut, R., and Schadow, H.: Klin. Wchnschr. **5**:1646, 1926.

If a patient is extremely fat or shows deficiency or suspension of sexual desire, metabolic disturbances are still revealed for a long time, although the psychosis may have disappeared.

The decrease in the basal metabolic rate reveals itself at any time from a few weeks to two months after the illness has begun.

In the beginning there is usually great loss of weight; as the psychosis is ameliorating or after it has disappeared, the patient gains in weight.

An increase in the basal metabolic rate during the psychosis can be regarded as prognostically favorable; a decrease during the psychosis with simultaneous increase in weight is prognostically unfavorable.

These alterations in metabolism follow their regular course regardless of the general condition of the patient.

The fact that there is a decrease in the specific dynamic action of protein in the beginning of schizophrenia was confirmed by Appel and Farr [3] in 1929. Other investigators (Henry [4]; Claude, Baruk and Medacovich [5]; Hoskins,[6] and Hoskins and Sleeper [7]), who determined the basal metabolic rate but not the specific dynamic action of protein, found a decrease in the basal metabolic rate only in many cases. These observations correspond with my results, as I also did not find a decrease in the basal metabolic rate in all cases, but, as mentioned, sometimes a decrease noted only in the specific dynamic action of protein.

It is important further to note that in cases of pure manic-depressive psychosis metabolic disturbances have never been found (repeated tests on 68 patients) unless the patient was suffering from another malady or was in the climacteric. The disturbance in metabolism is thus an indisputable differential criterion between cyclic psychosis and schizophrenia.

The technic of these investigations requires efficient apparatus, exacting methods of practice and sufficient experience, the results depending on the psychologic ability of the investigator. Only in such a way can one secure indisputable results. Every experiment in which the observations are not entirely free from objection must be repeated until the result is indisputable.

PERSONAL OBSERVATIONS

The results of researches of the Kestner school (Kestner, Liebeschütz-Plaut and Schadow [2]) indicated that the specific dynamic action of protein depends, at least in part, on the activity of the anterior lobe of

3. Appel, K. E., and Farr, C. B.: J. Nerv. & Ment. Dis. **70**:43, 1929.

4. Henry, G. W.: J. Nerv. & Ment. Dis. **70**:598, 1929.

5. Claude, H.; Baruk, H., and Medacovich, G.: Encéphale **23**:797, 1928.

6. Hoskins, R. G.: Oxygen Consumption ("Basal Metabolic Rate") in Schizophrenia: II. Distributions in Two Hundred and Fourteen Cases, Arch. Neurol. & Psychiat. **28**:1346 (Dec.) 1932.

7. Hoskins, R. G., and Sleeper, F. H.: Basal Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **21**:887 (April) 1929.

the pituitary gland and that when the specific dynamic action is decreased it can be raised by administration of anterior pituitary extract. Therefore, it was natural to administer such a preparation to patients suffering with schizophrenia.

At the start of my investigations I treated about 25 patients with praephyson, a preparation made from the whole anterior lobe of the pituitary gland. I could not see any certain effect on metabolism or the psychosis. Also, the use of roentgen rays and diathermy directed to the pituitary produced no positive changes. In 1931 I began to treat schizophrenic patients with praehormone, an extract of the urine of pregnant women.[8] In Breslau, Germany, 21 patients were treated. Although the changes in metabolism were not the same in every case, there was a constant tendency for the metabolism to return to normal. I continued treatment with this preparation in Panama, in 1936 and 1937, with 72 patients—34 women and 38 men. Unfortunately, I did not have the opportunity to study the metabolism of these patients.

The accompanying tables show the results obtained with this treatment:

TABLE 1.—*Results of Treatment of Patients in Breslau*

Duration of Psychosis	Complete Remission	Improvement	No Influence	Total No. of Cases
Less than ½ yr.	7	0	1	8
More than ½ yr.	8	2	3	13
Total no. of cases	15	2	4	21

TABLE 2.—*Results of Treatment of Women with Schizophrenia at Panama*

Duration of Psychosis	Complete Remission	Improvement	No Influence	Total No. of Cases
Less than ½ yr.	18	4	1	23
More than ½ yr.	7	2	2	11
Total no. of cases	25	6	3	34

TABLE 3.—*Results of Treatment of Men with Schizophrenia at Panama*

Duration of Psychosis	Complete Remission	Improvement	No Influence	Total No. of Cases
Less than ½ yr.	18	1	0	19
More than ½ yr.	2	10	7	19
Total no. of cases	20	11	7	38

8. Prepared by the Promonta Laboratories of Hamburg, Germany.

TABLE 4.—*Total Results of Treatments with Praehormone of All Patients in Breslau and Panama*

Duration of Psychosis	Complete Remission	Improvement	No Influence	Total No. of Cases
Less than ½ yr	42	6	2	50
More than ½ yr	17	14	12	43
Total no. of cases	59	20	14	93

TABLE 5.—*Percentage Values for All Patients Treated with Praehormone*

Duration of Psychosis	Complete Remission	Improvement	No Influence
Less than ½ yr	84	12	4
More than ½ yr	39.5	32.6	27.9
Average	63.4	21.5	15.1

COMMENT ON THERAPEUTIC RESULTS

The results reported were obtained with patients of different races: Twenty-one were white; 72 were colored and included mestizos (a mixture of Indian and white blood), mulattos, zambos (a mixture of Indian and Negro blood), pure Negroes and persons with a mixture of Negro, white and Indian blood, the last comprising the majority of the patients.

No difference between the therapeutic effects in the white and in the colored patients could be observed. An apparent inconsistency in results existed between the patients in Breslau and those in Panama, in the group of those who had full remissions after an illness of more than six months. Eight of 13 patients in Breslau, but only 9 of 30 in Panama, presented a complete remission. This can be explained simply as due to the fact that many of the patients in Panama had had the psychosis for a long time before treatment. If one compares the results in Breslau and those for the women with schizophrenia in Panama, one sees that they coincide. Of 11 women in Panama belonging to this category, 7 had complete remissions. Of these women, however, there were only a few with a psychosis that had lasted for many years. One sees, therefore, that the therapeutic results were about the same for the different races.

I was careful in evaluating my results, and when in doubt I counted the case as one in which there was improvement rather than as an instance of complete remission. It was not possible, however, to separate the material into cases in which there was a complete remission and those in which the patient was able to work. Most of the patients in Panama had no occupation. They came mostly from the interior of the country. Even when a patient had worked previously, it was impossible to discover whether he did again. For this reason, I differentiated only between those with complete remissions and those who improved.

The therapeutic results, as was shown in the majority of my cases, cannot be judged until some time after termination of the treatments. In a few cases the effect had already appeared during treatment, but these were exceptions. The shortest time in which one may form a definite opinion is two months after treatment has ended.

Comparison of my results with the number of cases of spontaneous remission and of improvement observed in patients with schizophrenia shows a much higher percentage with the treatment which I have described. Mayer-Gross [9] observed cure or improvement in 35 per cent of 245 cases at the Heidelberg Hospital; Otto-Martiensen [10] noted cures in 4.9 per cent and improvement in 28.8 per cent (together, 33.7 per cent) of 299 cases in Jena, Germany; Schmid [11] reported cures in 16.2 per cent and improvement in 15.5 per cent (together, 31.7 per cent) of 455 cases. Remission without treatment, therefore, is possible in from 31 to 35 per cent of cases. In my material one found, however, complete remission in 63.4 per cent and improvement in 21.5 per cent, which means that there is a possibility of improvement with this treatment in 84.9 per cent of cases.

The results may now be compared with those obtained by Dussik and Sakel and later investigators with the insulin treatment, and also with the effects of metrazol shock therapy reported by von Meduna. These results will first be compared on a purely numerical basis.

After adding the cases in which there was good remission and those in which there was complete remission, Dussik and Sakel [12] found 88 per cent of cases in which the duration of the psychosis was less than six months and the patient was able to work after discharge. Of the patients with disease of longer standing, 47.8 per cent were again able to work. Of the patients with complete remissions in my series, those with improvement being excluded, 84 per cent had disease of recent onset and 39.5 per cent disease of longer duration. The number of complete remissions obtained with the insulin treatment is less when the results of other investigators are taken into consideration. The average seems to lie at about 70 per cent when the disease was of recent onset and at 30 per cent when it was of long standing.

With regard to the results with metrazol shock treatment, von Meduna [13] reported remissions in 90 per cent of patients with recent subacute conditions and in 22.4 per cent of those with a chronic psy-

9. Mayer-Gross, W., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1932, vol. 9, pt. 5.

10. Otto-Martiensen, J.: Allg. Ztschr. f. Psychiat. **77**:295, 1921.

11. Schmid, H.: Schweiz. med. Wchnschr. **66**:960, 1936.

12. Dussik, K. T., and Sakel, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **155**: 351, 1936.

13. von Meduna, L.: Psychiat.-neurol. Wchnschr. **37**:317, 1935.

chosis. When the results of other investigators are considered, the percentage of remission obtained with this treatment is about 45 to 50.

The favorable results of my treatment, as far as can now be seen, numerically surpass those obtained with other methods. My method has also the advantage over the other two methods of not being dangerous to the patient. If the mental condition permits, the treatment can be given to ambulatory patients and in private practice.

If one considers the cases in my series in which the treatment had no effect, one finds that the condition was usually of the catatonic type. In some cases I treated catatonic patients with metrazol and injected praehormone on intervening days. Striking results sometimes occurred. Because of the limited amount of material available, I cannot conclude of what importance the injections of praehormone were in the improvement in these cases.

It is possible that insulin therapy can also be used as a complement to my method. I hope to show in further investigations to what extent the three methods can be used together. I believe, however, that this much can be said now: In every case of schizophrenia the praehormone treatment should be the method first used, as this procedure is in no way dangerous and the chances of cure are good. If no effect is obtained with this treatment, one of the aforementioned methods can be substituted, preferably metrazol treatment in cases of catatonic stupor, as far as I have been able to judge.

In the majority of cases an injection of praehormone on fifteen successive days is sufficient. If no improvement is observed three or four weeks after the last injection, a second series of fifteen injections should follow. I have generally not given more than fifteen injections in one course, in order to avoid injury to the sex glands. In special cases, however, one may exceed this amount.

In the cases of 2 patients treated in Panama relapses were noted several months after the therapy. I have been notified that 2 patients who were treated in Breslau in 1934 are still well and able to work. It is impossible to form any opinion as to the duration of the cure because the time has been too short and it is difficult to obtain information about patients treated in Germany and Panama.

THEORETIC CONSIDERATIONS

I believe that the fundamental difference between insulin and metrazol shock treatments, on the one hand, and my method, on the other, depends on the fact that my treatment is one which influences the causal mechanism. As the cause of schizophrenia is not known, one cannot speak of causal therapy, nor dare one speak of specific therapy. It seems probable, nevertheless, that something more than a symptomatic effect is secured with the praehormone.

As has already been described in detail, the primary disturbance of the gaseous metabolism in schizophrenia consists of diminution in the specific dynamic action of protein. The particular substance which raises the specific dynamic action is a hormone from the anterior lobe of the pituitary body. I have assumed from the beginning, therefore, that, especially in the early forms of the disease, the metabolism can be influenced by administering a substance from the anterior lobe of the hypophysis. I have assumed, in accordance with the opinion expressed by Aschheim and Zondek and by many other authors, that there are hormones similar to those of the anterior lobe of the pituitary gland in the urine of pregnant women, and I used, therefore, a preparation which is extracted from such urine.

The opinion that this therapy is more than symptomatic is further supported by experiments of Turkevich and Gershanovich.[14] They found that the amount of gonadotropic substance (which is similar to one of the hormones secreted by the anterior lobe of the pituitary gland) in the blood of schizophrenic patients is decidedly less than that of normal persons. This means that my assumptions receive confirmation from an altogether different source.

The metabolic changes which I was able to establish in the cases observed in Breslau after injections of praehormone have given no indication as to its method of functioning. One sometimes finds a rise in the specific dynamic action of protein, but sometimes the basal metabolic rate is increased; at present, therefore, because of insufficient material, I cannot say anything about the effect of praehormone on the specific dynamic action and the basal metabolic rate. Today I know only that values for both have a tendency to return to normal some time after termination of the injections.

An explanation is also difficult because one does not know the influence of the anterior lobe of the hypophysis on the general metabolism. It is known that generally the specific dynamic action of protein rises and the basal metabolic rate falls when a preparation of the anterior lobe of the pituitary gland is administered. One does not know, however, why the basal metabolic rate falls.

In observing the effects of a single dose of praehormone on the basal metabolic rate and the specific dynamic action of protein in normal and in schizophrenic persons, such variable results have thus far been obtained that no definite conclusions are possible. Finally, I have no idea what hormones, in addition to the one regulating metabolism, are contained in this preparation. According to the investigations of Falta and Högler,[15] praehormone contains, in addition to the gonadotropic sub-

14. Turkevich, O. M., and Gershanovich, Z. S.: Sovet. psikhonevrol., 1936, no. 6, p. 80.

15. Falta, W. S., and Högler, F.: Klin. Wchnschr. **9**:1807, 1930.

stance, a hormone for growth, and it is also probable that it stimulates the function of the thyroid.

For all these reasons it was not possible to include substances similar to praehormone in my investigations without extending the experiments immeasurably. Despite the more or less similar manner of manufacturing preparations from the urine of pregnant women, it is probable that products from different firms may not have the same effect. To mention one example, Anselmino and Hoffmann [16] found that there is hardly any metabolic hormone in the commercial product prolan (I. G. Farben Industrie), an extract from the urine of pregnant women containing a large amount of gonadotropic substance. I cannot say, therefore, that the same results which I have obtained with praehormone can be obtained with similar preparations. The aim of further investigations will be to determine this.

Investigation of the metabolism can therefore give no information as to the way in which substance from the anterior lobe of the pituitary body or anterior pituitary-like substances act on the psychotic process in schizophrenia. As Bernhardt [17] has shown in regard to praephyson in other diseases, I can say only that praehormone has a tendency to cause both the basal metabolic rate and the specific dynamic action of protein to return to normal. The return of both occurs, however, a few weeks after termination of the treatment, simultaneously with improvement, i. e., with remission. It is not altogether strange that the effect on metabolism and that on the psychosis do not occur instantaneously when one considers that even after castration metabolic changes take place some time after the operation.[18]

CONCLUSIONS

1. In every case of schizophrenia there is a disturbance in the gaseous metabolism, which begins with decrease in the specific dynamic action of protein.

2. The specific dynamic action of protein depends, at least in part, on secretions from the anterior lobe of the pituitary gland.

3. The treatment of schizophrenic patients with an extract containing anterior pituitary-like substances from the urine of pregnant women produces good therapeutic results, and has the added advantage of not being a dangerous form of therapy.

21 Buena Vista Avenue, San Francisco.

16. Anselmino, K. J., and Hoffmann, J.: Klin. Wchnschr. **10**:2380, 1931.

17. Bernhardt, H.: Klin. Wchnschr. **9**:399, 1930.

18. Rolly: Deutsche med. Wchnschr. **47**:887 and 917, 1921. Fischer, S.: Klin. Wchnschr. **6**:2239, 1927. Liebesny, P.: ibid. **4**:156, 1925.

CAPILLARY STRUCTURE IN PATIENTS WITH SCHIZOPHRENIA

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The character of the cutaneous capillary structure in 1,100 schizophrenic persons was studied for the purpose of ascertaining whether a distinction can be made between the capillary structure in normal persons and that in persons with schizophrenia.[1]

Investigation of the role of the capillaries has for the most part been restricted to pointing out analogies between the balanced arteriovenous circulation and growth. Stricker,[2] as early as 1865, described the structure and function of the capillaries; Rouget,[3] in 1873, the developmental properties of the capillaries, and Ray and Brown,[4] in 1879, the capillaries in relation to blood pressure. Since that time many studies on capillary function have been reported; for example, Aby [5] discussed the effect of capillary function on circulation in the brain; Bremer [6] wrote on the nerve connections of the capillaries, and reports continue to appear on the role the capillaries play in the general process of tissue metabolism.

More recently, Krogh,[7] Ebbecke,[8] Thaller and von Draga,[9] Tinel and Ungar,[10] Krogh and Harrop,[11] Basler,[12] Hooker,[13] Lewis [14] and

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From the Psychiatric Institute, University of Illinois College of Medicine; Dr. H. Douglas Singer, Director.

1. Observation of capillary structure was selected for the following reasons: It offers simplicity of approach, since nothing artificial is added; previous studies of the capillary system in relation to health and disease have shown it to be a good index of bodily function.

2. Stricker, S.: Studien über den Bau und das Leben der kapillaren Blutgefässe, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **52**:379, 1865.

3. Rouget, C.: Mémoire sur le développement, la structure et les propriétés physiologiques des capillaires sanguines et lymphatiques, Arch. de physiol. norm. et path. **5**:603, 1873.

4. Ray, C. S., and Brown, J. G.: The Blood Pressure and Its Variations in the Arterioles, Capillaries and Small Veins, J. Physiol. **80**:223, 1879.

5. Aby, F. S.: Observations on the Blood Capillaries in the Cerebral Cortex of Normal Young Adult Domestic Cats, J. Comp. Neurol. **9**:26, 1899.

6. Bremer, L.: Die Nerven der Kapillaren, Arch. f. mikr. Anat. **21**:663, 1882.

7. Krogh, A.: The Number and Distribution of Capillaries in Muscles with Calculations of the Oxygen Pressure Necessary for Supplying the Tissue, J. Physiol. **52**:405, 1919.

8. Ebbecke, U.: Physiologie der Capillaren, Naturwissenschaften **14**:1131, 1926.

others have contributed further to knowledge of the significance of capillaries in tissue changes. Weiss and Holland,[15] Tannenberg,[16] Zimmermann [17] and Vimtrup [18] reported on the anatomic and morphologic aspects of the capillary. Recently, Jaensch and Wittneben,[19] Müller,[20] Wichura,[21] Sepp,[22] Parrisius,[23] Lewis [14] and Pickworth [24] have discussed the relationship of the capillaries to health and disease. Observations on the capillary structure of the finger nail bed in feebleminded children were made by Jaensch,[25] and Leonhard [26] reported on the correlation between

9. Thaller, L., and von Draga, E.: Zur diagnostischen Verwertbarkeit der mikroscopischen Hautkapillaren Untersuchungen am lebenden Menschen, Wien. klin. Wchnschr. **30**:686, 1917.

10. Tinel, J., and Ungar, G.: La régulation de la circulation cérébrale, Presse méd. **44**:169, 1936.

11. Krogh, A., and Harrop, G. A.: On the Substance Responsible for Capillary Tonus, J. Physiol. **54**:cxxv, 1921.

12. Basler, A.: Ueber die Blutbewegung in der Kapillaren, Arch. f. d. ges. Physiol. **171**:134, 1918.

13. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol. **54**:30, 1920.

14. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1929.

15. Weiss, E., and Holland, M.: Zur Morphologie und Topographie der Hautkapillaren, Ztschr. f. exper. Path. u. Therap. **22**:108, 1921.

16. Tannenberg, J.: Bau und Function der Blutkapillaren, Frankfurt. Ztschr. f. Path. **34**:1, 1926.

17. Zimmermann, K. W.: Die feinere Bau der Blutkapillaren, Ztschr. f. d. ges. Anat. **68**:29, 1925.

18. Vimtrup, B.: Beiträge zur Anatomie der Kapillaren: I. Ueber contractile Elemente in der Gefässwand der Blutkapillaren, Ztschr. f. d. ges. Anat. **65**:150, 1922.

19. Jaensch, W., and Wittneben, W.: Archikapillaren endokrines System und Schwachsinn, in Bericht über den Kongress für Heilspädagogik, Berlin, Julius Springer, 1925.

20. Müller, O.: Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen, Stuttgart, Ferdinand Enke, 1922.

21. Wichura, C.: Thymogene Kapillaratonie als Ursache cerebraler Störungen, J. f. Psychol. u. Neurol. **37**:401, 1928.

22. Sepp, E.: Die Dynamik der Blutzirkulation im Gehirn, Berlin, Julius Springer, 1928.

23. Parrisius, J.: Kapillarstudien bei Vasoneurosen, Deutsche Ztschr. f. Nervenh. **72**:310, 1921.

24. Pickworth, F. A.: A New Method of Study of the Brain Capillaries and Its Application to the Regional Localization of Mental Disorders, J. Anat. **69**:62, 1934.

25. Jaensch, W.: Ueber psychophysische Konstitutionstypen, München. med. Wchnschr. **35**:1101, 1921.

26. Leonhard, K.: Ueber kapillarmikroskopische Untersuchungen bei zirkulären und schizophrenen Kranken und über die Beziehungen der Schlingenlänge zu bestimmten Characterstrukturen, Psychiat.-neurol. Wchnschr. **30**:487, 1928.

the capillary loops of the finger nail bed and the mental characteristics of patients with schizophrenia.

A survey of the literature, however, does not reveal specific reports on quantitative measurements, unit descriptions or a comparative study of large groups of healthy and mentally ill persons over a number of years.

NORMAL APPEARANCE OF CAPILLARIES

1. *The Unit.*—A capillary is a vascular unit the caliber of which is sufficient to permit a single erythrocyte to pass through without producing a structural deformation of the cell and without permanent distortion of the capillary wall (fig. 1).[27]

2. *Size.*—In normal young persons the capillary in the area studied is shaped like a comma; it is of uniform caliber, and its width is that of a normal red blood corpuscle, corresponding approximately to 6 microns. What is seen is the

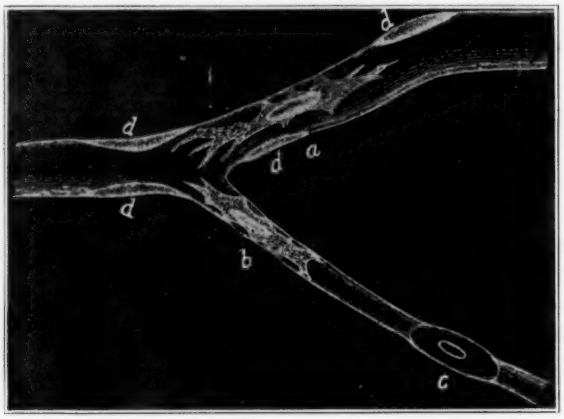

Fig. 1.—In this drawing, *a* and *b* indicate contracting Rouget cells, as seen on capillaries in living newt larvae; *c*, an elongated red blood corpuscle, and *d*, endothelial cells. × 500; after Vimtrup.[18]

arch. The uniformity of appearance of the arch allows it to be used as a unit of comparison (fig. 2).

3. *Number.*—The normal number of capillaries in the area of skin studied is from 50 to 70 per 5 mm. square of a blood counting chamber.

4. *Color.*—The color of the capillaries approximates that graded from 50 to 80 on the Tallqvist hemoglobin scale.[28]

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27. The capillary wall consists of the lining plates, endothelial cells and Rouget cells. While the structure of the capillary is still controversial, it is generally accepted that the endothelial cells contribute toward nutrition and the Rouget cells toward the maintenance of tonus (fig. 1).

28. This is not considered as an exact color value, but in studying a large control group, as was done in this investigation, the color approximation has definite value and has been designated as the "capillary color value."

5. *Arrangement and Distribution.*—In normal persons the capillaries in the area studied are characteristic in arrangement, distribution and morphologic features (fig. 2). Abnormal units of types to be described are not seen.

6. *Stream.*—In normal persons the flow through the capillary is without interruption and maintains a relatively uniform speed.[29]

7. *Tonus.*—In normal persons in the sitting, standing or reclining postures no contraction or dilatation of the capillaries is seen.

Summary.—A norm has been obtained from a previous study [30] of nearly 6,000 apparently healthy persons of all ages, including newborn infants immediately after delivery by cesarean section. From this group were taken 1,058 persons comparable in age with the 1,047 schizophrenic persons studied. Each was scored on the basis of the seven normal characteristics outlined.

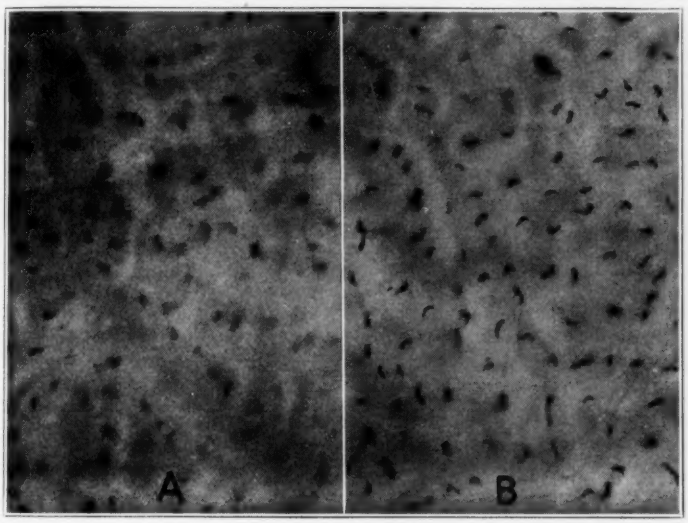

Fig. 2.—Photomicrographs showing the predominance of comma-like capillaries in the normal subject. *A* is not retouched; *B* is retouched to emphasize the normal arrangement, comma-like structures and uniform distribution. It should be noted that the photographs do not show the capillaries as distinctly as they are seen by direct observation.

MATERIAL AND METHODS

Two thousand subjects suffering from psychoses were studied at the following institutions: the Psychiatric Institute of the University of Illinois and the

29. Analysis of the material indicates that a direct relation exists between the rate of flow in the capillary and its contractibility.

30. Olkon, D. M.: Genuine Epilepsy: Studies of the Microscopic Changes in the Capillary System as a Probable Etiologic Factor, J. Nerv. & Ment. Dis. **72:** 538, 1930.

Chicago, Elgin and Dixon State Hospitals. From this group 1,100 patients with psychoses diagnosed as schizophrenia were selected for this report. The investigation was carried out during the period from May 1932 to June 1938. Many patients in the Psychiatric Institute were reexamined at intervals of from two to four weeks, and the capillary fields were compared with changes in general health, behavior and mental condition.

Observations were made in the triangular space on the dorsum of the hand bounded by the first and second metacarpal bones and the free edge of the skin between the thumb and the index finger. This area was found to be the most accessible and uniform for observation. The nail bed, ordinarily used, is less desirable for comparative studies, since the changes under the nail bed are misleading and unreliable because the loops are compressed and stretched out.

The capillaries were measured by a micrometer scale on which 0.5 mm. is so divided that each space between two vertical lines equals the diameter of a red blood cell (approximately 6 microns). The scale is set into a special 7 × ocular of the capillary microscope.

The graduated disk used for counting the capillaries was similar to that of a blood counting chamber. Each 5 mm. square is divided into 10 equal divisions, with a total of 100 squares. The disk was set into a no. 6 *Kompens Okular* in the Zeiss capillary microscope. The number of capillaries in each square was counted; three counts were made, and the average of the three counts was used.

Observations were made with a Zeiss skin microscope with a 60 × objective and a 10 × ocular, which contains a 6 volt lamp inside the tube.[31] Extraneous light was excluded by a soft rubber ring at the end of the tube, which hugs the skin. Immersion oil was spread over the part to be examined.

The large tube microscope of Zeiss, with a Bausch & Lomb objective (22.7 mm.; numerical aperture, 0.17; 6 ×) was used for photographs; this gives a magnification similar to that of the skin microscope. A Leitz Leica camera with a special lighting device was attached to the microscope.[32] The stage of the microscope was specially constructed for this work.

A Pachon oscillometric sphygmomanometer, a modified type of aneroid plethysmograph and manometer combined, was used for compression of the vessels of the upper part of the arm. This permitted observation of the effects on the capillaries of all postures and all degrees of compression. It is calibrated in centimeters and gives a fairly accurate measure of the pulsation in the main arteries; when these are occluded no oscillation is visible.

Rating.—When each of the seven characteristics was present with no abnormality the score was 100; deductions from a perfect score were made on the basis of deficits in each of the points considered. For example, each characteristic scored one-seventh of 100 per cent, or 14.2 per cent. If the number of capillaries or their size or color value was half that of the normal the characteristic scored only one half of 14.2 per cent, or 7.1 per cent. The results for each person were tabulated, and each characteristic was scored individually, in separate columns. On the basis of these tabulations the average score for the healthy group was

31. The smaller magnification was chosen to obtain a larger field of observation and to lessen the number of artefacts.

32. Photographing through the skin does not give a sharp, vivid reproduction of the capillaries. It was necessary, therefore, to retouch these photographs for clearness, but nothing new was added. Dr. C. W. Darrow, of the Institute for Juvenile Research, aided in the photography.

73 per cent. This was used for a comparative determination of deviations in this study (table, A and B).

All the observations enumerated were made on each patient.

OBSERVATIONS

In patients with schizophrenia the cutaneous capillaries showed striking deviations from the normal. There were: reduction in number; few comma shapes; a paler color; lack of uniformity in size, and a variety of bizarre shapes—spiral, crescent, hairpin-like and stellate forms and dilated, ameboid forms with pseudopodia (fig. 3). Moreover, the flow through the capillaries was seldom uniform; at times it was more rapid, and at times slower, than normal; at other times the contractions and dilatations were outstandingly irregular (fig. 4). Another striking feature was the frequent occurrence of capillary hemorrhage in excited schizophrenic patients (fig. 5). In patients with hebephrenia of long standing sparseness of capillaries was the most marked feature, aside from the bizarre shapes mentioned previously (fig. 6). It is important to note that these changes occurred in schizophrenic patients, whereas in normal persons of similar age they were absent.[33]

To illustrate the capillary changes, 2 cases are reported.

REPORT OF CASES

CASE 1.—A boy aged 12 years was admitted to the Psychiatric Institute from the Institute for Juvenile Research because of a behavior problem. Examination of the cutaneous capillaries soon after admission showed: color value, 30 (Tallqvist scale); size from less than 1 to over 2 spaces on the scale; number, 10 in a 5 mm. square, and absence of comma forms from the field. The few capillaries were scattered. All the capillaries were distorted, and hairpin-like, spiral, stellate, looped and greatly dilated forms were present. In summary, there were sparsity of capillaries, reduction in color and bizarre units, such as have already been described.

Four months later, mutism, negativism and catatonic features became pronounced, and the patient was transferred to the Elgin State Hospital. Two years later, a second examination at this hospital was reported on as follows: "The patient was listless and pale; saliva drooled from his mouth, and he showed flexibilitas cerea. He appeared greatly deteriorated, both physically and mentally. Microscopic examination of the capillaries showed marked sparsity of capillaries and absence of comma-like forms; the few capillaries in the field were pale, with many of the abnormal units described previously; the stellate forms were more numerous than before."

CASE 2.—This case, that of a youth aged 20, illustrates the apparent permanence of the capillary defects and their relation to the severity of the mental disorder.

33. Later in this study patients over 25 were excluded, for after that age capillary changes in other bodily diseases are common, particularly in cardiovascular-renal disease, diabetes, vasomotor and trophic disturbances and progressive sclerosis.

Fig. 3.—Drawing showing some of the outstanding bizarre capillary forms seen in young schizophrenic patients: *a*, dilated, ameboid forms; *b*, crescent-like forms; *c*, a hairpin-like form; *d*, a spiral form; *e*, a stellate form, and *f*, extremely dilated capillaries, partially filled with blood.

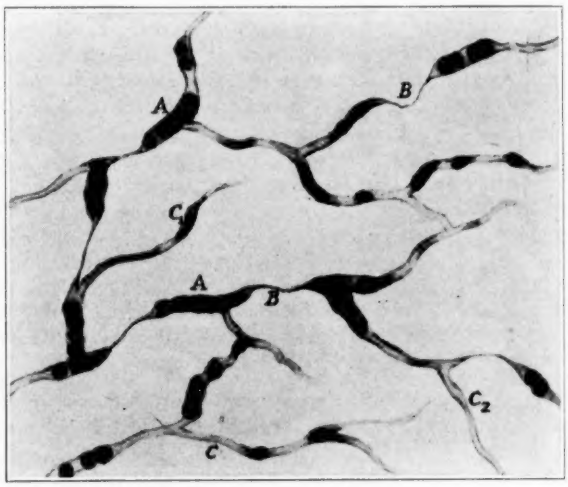

Fig. 4.—Drawing showing pronounced contraction and dilatation of the capillaries, often observed in schizophrenic patients. *A*, dilatation; *B*, extreme contraction; C_3, normal capillary; C_1, capillary going into contraction, and C_2, empty space in a capillary.

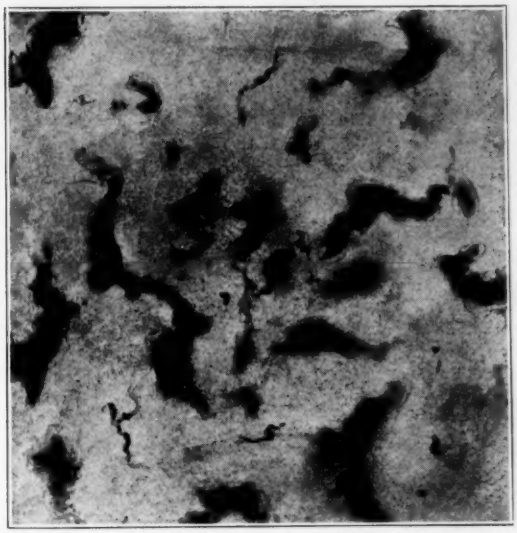

Fig. 5.—Drawing showing capillary hemorrhages often observed in hyperactive schizophrenic patients.

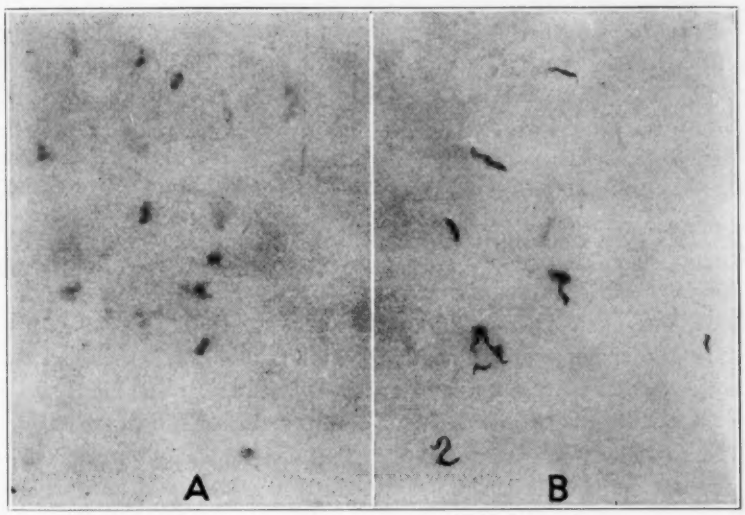

Fig. 6.—Photomicrograph showing sparsity and deformation of capillaries. *A* is not retouched; *B* is retouched. The slight difference in the two areas is due to the curving of the area under observation, of which the portion *B* is not in sharp focus.

Examination of the cutaneous capillaries on admission showed: color value, 30 (Tallqvist scale), the capillaries appearing almost colorless; size, barely 1 space on the scale; number, 15 in a 5 mm. square; many pinpoint forms; no comma-like forms; some crescent-shaped, some stellate and some spiral units, and some forms that were difficult to describe.

The impression was that of marked deficit in nearly all values of the capillary units.

The patient became mute, was fed with a tube and seemed oblivious to his surroundings. The striking defect of the capillaries, their sparsity and the presence of bizarre units in so young a person, who was apparently free from other organic disease, connoted a severe type of capillary disorganization. He was reexamined at intervals of about a week for eight months. The capillary picture throughout remained similar to that already described, with the stellate forms becoming more numerous and the number of capillaries decreasing.

The patient has received treatment with insulin and metrazol shock, hyperthermia and prolonged sleep. Improvement has been negligible. At times there have been short periods of slight amelioration of symptoms, but the patient soon reverts to his former state.

COMMENT

Observations on young schizophrenic patients seem to indicate the presence of capillary inadequacy and disharmony. Pickworth's [24] statement that the remarkable evenness of the normal capillary in all its phases is "a valid reason for attaching importance to this condition" is corroborated by this study. Regularity of the capillaries in the internal organs as well as in the skin of the healthy living dog has been reported.[34]

The cases cited are representative of the more extreme capillary changes in schizophrenia, but in the entire group there were sparseness of capillaries, reduction or absence of comma-like structures, reduction in color and the presence of novel units, not usually seen in normal persons. The most impressive feature was the progressive development of stellate, spiral and crescent forms as the disease progressed. Moreover, there was present tortuosity of the capillaries resembling that of arteriosclerosis (fig. 7). In some cases the comma-like structures increased in number as the patients improved, but the abnormal units described showed little change; it was concluded that this indicated a permanent defect. The changes in the capillary units in the 2 cases cited suggest that there was apparently a constitutional factor which influenced metabolic function and the development of the disease.

"Mental functions are absolutely dependent upon the integrity of the supply of blood in the brain," said Trotter.[35] Since the brain depends

34. Olkon, D. M., and Joannides, M.: Capillaroscopic Appearance of the Pulmonary Alveoli in the Living Dog, Anat. Rec. **45**:121, 1930.

35. Trotter, W., in Choyce, C. C.: A System of Surgery, London, Cassell & Co., 1914.

on the general circulation for its supply of blood and since the capillaries are the final conveyors of all nutritive elements and materials for gaseous exchange, it follows that a chronic deficit in the capillaries, when extensive, must also affect the brain.

It is striking how closely related the results of Müller's [36] study on the peripheral capillaries in health and disease are to those of Bruns and König,[37] Hooker,[13] Krogh,[38] Langley,[39] Ricker and Regendanz,[40] Zak,[41] Tinel [42] and others, who asserted that the capillaries manifest greater vegetative imbalance in persons with capillary inadequacy. These authors asserted, further, that in cases of such disturbance the

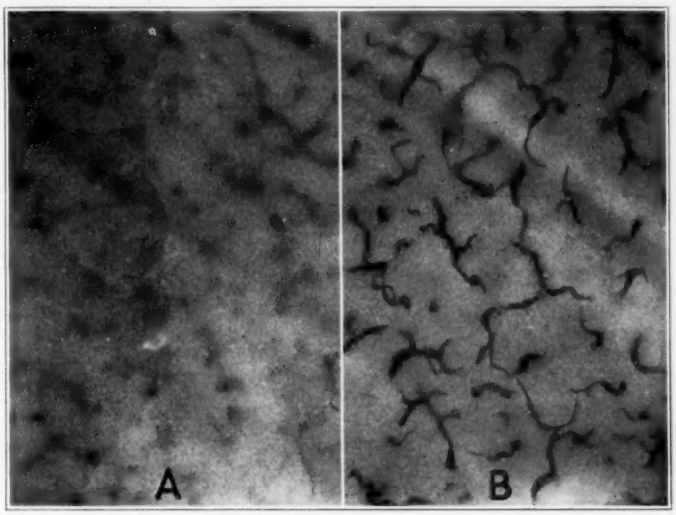

Fig. 7.—Photomicrograph showing marked changes of the capillaries and venules, resembling sclerotic manifestations. *A* is not retouched; *B* is retouched.

36. Müller, O.: Zur Beobachtung des Kapillarkreislaufs beim Menschen, Verhandl. d. deutsch. Kong. f. inn. Med., 1920, p. 211.

37. Bruns, O., and König, F.: Ueber die Strömung in den Blutkapillaren der menschlichen Haut bei kalten und warmen Bädern und über die "Reaktion" in und nach kühlen Wasser- und Köhlensäurebadern, Ztschr. f. Phys. u. diätet. Therap. **24**:1, 1920.

38. Krogh, A.: The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation, J. Physiol. **52**:457, 1919.

39. Langley, J. N.: The Vascular Dilatation Caused by the Sympathetic and the Course of Vasomotor Nerves, J. Physiol. **58**:70, 1923.

40. Ricker, G., and Regendanz, P.: Beiträge zur Kenntnis der örtlichen Kreislaufsstörungen, Virchows Arch. f. path. Anat. **231**:1, 1921.

41. Zak, E.: Ueber den Gefässkrampf bei intermittierendem Hinken und über gewisse kapillomotorische Erscheinungen, Wien. Arch. f. inn. Med. **2**:405, 1921.

42. Tinel, J.: Réalité clinique et probabilités physiologiques d'une vasomotricité cérébrale: Les systèmes régulateurs de la circulation cérébrale, Rev. neurol. **65**:1255, 1936.

endogenous, as well as the exogenous, elements accentuate vascular imbalance and help to promote disease conditions. In other words, tissue metabolism, in which the capillaries play a part, is intimately connected with tissue activity, including the activity of the brain. Hence, Devine's [43] statement that dementia praecox is a failure not so much of intellect as of a vital center is pertinent.

Obviously, capillary function may be affected by numerous conditions, such as the degree of blood flow, state of muscle tone, blood

Mean Values for Capillaries in Schizophrenic and Normal Persons *

Age Group, Yr.	Mean Number of Capillaries per 5 Mm. Square	Mean Color Value (Tallqvist Scale)	Mean Minimum Size	Mean Maximum Size
	A. Schizophrenic Persons			
Under 25.....	24.82 (395 patients)	41.50 (317 patients)	4.02 microns (314 patients)	9.48 microns (310 patients)
Over 25.....	21.88 (642 patients)	40.85 (521 patients)	3.72 microns (510 patients)	9.24 microns (503 patients)
Total group..... (1,047 patients)	22.78	41.10 (838 patients)	3.83 microns (824 patients)	9.33 microns (813 patients)
	B. Normal Persons †			
Under 25.....	48.22 (486)	60.50 (486)	Approximately 1 division on the scale‡	Approximately 1 division on the scale
Over 25.....	41.64 (570)	54.80 (570)	Approximately 1 division on the scale	Approximately 1 division on the scale
Total group (1,056).....	44.93	57.65	Approximately 1 division on the scale	Approximately 1 division on the scale

* The sizes of the capillaries as given in this table are approximations only, since observations with the calibrated scale within the *Okular* cannot be determined with accuracy. All that is indicated is the tendency to capillary disharmony in schizophrenia.

Differences in the number of cases for each of the values established are due to the fact that in the beginning of the study different factors were thought to be of greater importance.

† The 1,056 subjects in B were taken as a comparable sample from a normal group of about 6,000.

‡ One division on the scale equals approximately the diameter of a normal red blood corpuscle, namely, 6 microns.

pressure and heart rate. My study, however, was carried out on a large group of schizophrenic patients, in whom the bodily diseases mentioned were not present and therefore could scarcely have been the major feature in producing the definite cutaneous capillary deficiency and typical morphologic abnormalities of the capillaries which were observed. These are summarized in the accompanying table.

Parts A and B of the table, showing mean values, indicate clearly how the values for the majority of schizophrenic patients considered in this study deviated from the norm; for example, the number of cap-

43. Devine, H.: The Problem of Schizophrenia, Proc. Roy. Soc. Med. **26**:111, 1932.

illaries for the majority of patients in the schizophrenic group lies far below the mean values for normal persons. The lack of comma-like units, the reduction in color and the irregularity in size are also apparent.

The main concern of this study was the correlation of the cutaneous capillary structure with abnormal behavior. Many vegetative and metabolic disturbances were also noted, but are not incorporated in the report.

At first glance the schizophrenic patient presents, in many instances, a status different from that of the average person in normal health. His metabolism is subject to great fluctuations; for example, he displays changes in energy output; youthful patients with hebephrenia and schizophrenia simplex show signs of premature exhaustion physically as well as mentally. The concept of premature senility seems to fit this picture. The brain of a schizophrenic person acts for the most part like an exhausted brain. These characteristics are much more in evidence when an anlage or an endogenous component seems to exist. Whether the vascular imbalance noted in the cases studied is the ultimate result of the psychosis or whether the psychosis is the expression of metabolic changes indicated by the observed structural changes in the capillaries, such as variations in size, number and color, cannot be definitely stated. These changes, nevertheless, are intimately associated with the disease. Furthermore, repeated observations on schizophrenic patients have shown that the capillary disorganization progresses as the disease advances.

It is not intended to imply that a definite diagnosis of dementia praecox, or of any other disease, can be made from a study of the capillaries alone, since the changes they show are only a part of the complex pattern of the disease. If the observations in this study are corroborated, however, one may predict that when other indications of the severity of the illness are not available one may obtain confirmation of the condition from a study of the capillaries.

From the findings it is clear that in organic and vegetative derangements there are definite disturbances in the capillaries which may be corroborative evidence for the increasingly accepted theory that schizophrenia is a vegetative and metabolic disorder.

SUMMARY AND CONCLUSIONS

1. Schizophrenia is associated with a defect in the capillaries.

2. The observations indicate that the severity of the disease is related to the degree of derangement of the capillary structure.

3. The studies suggest that schizophrenia falls in the category of vegetative and metabolic disorders.

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LESIONS OF THE FUNDUS ASSOCIATED WITH BRAIN HEMORRHAGE

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There is a general unawareness among clinicians of the incidence of ocular disturbances following hemorrhage of the brain. These complications have been recognized for fifty years or more; yet they have attracted comparatively little interest. Elschnig [1] expressed the belief that such changes are rare and that, when they appear, the level of the intracranial pressure bears no relation to them. In several of Elschnig's cases the fundi were normal, although at autopsy bleeding into the optic sheaths was demonstrated. Thyme,[2] Spiller,[3] Taylor,[4] Pearce,[5] Gordon,[6] Hawthorne,[7] Polstroff [8] and Meyer [9] described cases of intraventricular hemorrhage, but failed to mention the condition of the

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1. Elschnig, A.: Ueber die pathologische Anatomie und Pathogenese der sogenannten Stauungspapille, Arch. f. Ophth. **41**:179, 1895; Bemerkung zur der Mittheilung Schnaudegels: Ein Fall von multiplen Blutungen des Sehorgans, ibid. **48**:461, 1899.

2. Thyme, W.: A Case of Cerebellar Haemorrhage Presenting Well-Marked Early Cervical Opisthotonos and Kernig's Sign, Lancet **1**:397, 1901.

3. Spiller, W. G.: Duration of Life After Extensive Hemorrhage of the Brain, J. A. M. A. **51**:2101 (Dec. 19) 1908.

4. Taylor, H.: Non-Traumatic Cerebral Hemorrhage in a Child, Lancet **1**: 291, 1905.

5. Pearce, T. M.: A Fatal Case of Cerebral Hemorrhage in a Youth, Lancet **2**:1321, 1902.

6. Gordon, A.: Ventricular Hemorrhage: A Symptom Group, Arch. Int. Med. **17**:343 (March) 1916; Primary Ventricular Hemorrhage: Further Contribution to Characteristic Symptom Group, Arch. Neurol. & Psychiat. **39**:1272 (June) 1938.

7. Hawthorne, C. O.: Cerebral and Cerebellar Hemorrhages in Apparently Healthy Adolescents and Children, Practitioner **109**:425, 1922.

8. Polstroff, F.: Tödliche Blutung in das Ventrikelsystem bei Hirnabszess aus der Abszessmembran, Centralbl. f. d. allg. Path. u. path. Anat. **60**:371, 1934.

9. Meyer, E.: Zur Kenntnis der pialen und Ventrikel-Blutungen, Arch. f. Psychiat. **81**:595, 1927.

eyegrounds. In Hird's [10] case the disks appeared normal, but the retinal veins were congested. Winkelman and Eckel's [11] series consisted of 30 cases of massive hemorrhage of the brain, in the majority of which the ventricular system had been involved; yet in 1 case only choked disks in which there was pontile bleeding were described.

Priestly Smith [12] did not observe alterations in the retinas or optic disks eighteen hours before death from extensive subarachnoid hemorrhage, despite the presence of blood in the optic nerve sheaths. However, such was not the experience of others. Symonds,[13] Bramwell,[14] Mott and Stedman [15] and Smith [16] described papilledema, retinal venous engorgement and subretinal and punctate retinal hemorrhages following subarachnoid hemorrhage. Riddoch and Goulden [17] found papilledema the most constant ocular complication of subarachnoid hemorrhage; it was said by these authors to have been mentioned in almost all reports except those of Smith [12] and Elschnig.[1] The swelling of the disks is usually mild, although Rollet [18] reported 1 case of marked papilledema. Retinal hemorrhages were regarded by Riddoch and Goulden as less constant than changes in the disks; the hemorrhages do not necessarily occur bilaterally and are usually characterized by small foci of bleeding near the disks. Symonds analyzed the ocular findings in 14 cases of subarachnoid hemorrhage (in a series of 124) in which the fundi were examined. In 2 cases the fundi were normal; in 3 there were subhyaloid hemorrhages; in 3 only unilateral hemorrhages occurred; in the remaining 6 cases the retinas were free from bleeding, but various degrees of papillary swelling had occurred. Anatomic examinations of the optic nerves demonstrated constant

10. Hird, A. E. W.: A Case of Cerebellar Hemorrhage, Lancet **2**:734, 1910.

11. Winkelman, N., and Eckel, J.: Extensive Brain Hemorrhage, J. Nerv. & Ment. Dis. **61**:593, 1925.

12. Smith, P.: Cerebral Haemorrhages with Passage of Blood into Both Optic Nerves, Tr. Ophth. Soc. U. Kingdom **4**:271, 1884.

13. Symonds, C. P.: Spontaneous Subarachnoid Hemorrhage, Quart. J. Med. **18**:93, 1924.

14. Bramwell, cited by Symonds.[13]

15. Mott and Stedman, in discussion on Bellamy, W.: Aneurysm of the Anterior Communicating Artery; Ruptured; Meningeal Haemorrhage Accompanied by Optic Neuritis, Lancet **2**:15, 1889.

16. Smith, F. W. G.: Intraocular Changes Suggesting Spontaneous Subarachnoid Hemorrhage in a Case of Apoplexy, Irish J. M. Sc., 1930, p. 157.

17. Riddoch, G., and Goulden, C.: On the Relationship Between Subarachnoid and Intraocular Hemorrhage, Brit. J. Ophth. **9**:209, 1925.

18. Rollet, cited by Riddoch and Goulden.[17]

bleeding into the optic nerve sheaths. This led to the interpretation by Daubler and Marlow [19] of an escape of blood from the sheaths through the lamina cribrosa into the retinas. Symonds, Mott and Stedman and Bramwell stated that the anatomic relationship of the sheaths (Schwalbe [20]) seemed to make such an interpretation unlikely. These authors expressed the belief rather, that the central vein of the retina, emerging from the optic nerve, was compressed in the sheaths by the blood extravasated there and that the resulting retinal venous stasis produced bleeding.

Intracerebral hemorrhage not infrequently presents a problem of differentiation from tumor of the brain. Such cases have been described by Globus and Strauss.[21] Sachs [22] commented that "even in the presence of choked disk [we should] bear in mind that hemorrhage . . . may cause symptoms suggestive of tumor." Harris [23] removed a blood clot in his search for tumor in a case of progressive papilledema. Penfield [24] and Craig and Adson [25] mentioned papillary changes in several patients with cerebral hemorrhage. Stough [26] said that differentiation of choked disk and the retinitis of cardiovascular disease is a difficult task and described several cases of the latter in which there were papilledema and retinal hemorrhages.

Twenty-three cases of cerebral hemorrhage with papillary swelling and retinal bleeding are reviewed in this report. In 2 cases serious consideration was given to the differential diagnosis of tumor of the

19. Daubler, F. H., and Marlow, S. B.: A Case of Hemorrhage into the Optic Nerve Sheaths as Direct Extension from a Diffuse Intrameningeal Hemorrhage Caused by Rupture of Aneurysm of a Cerebral Artery, Arch. Ophth. **46**:533, 1917.

20. Schwalbe, G.: Lehrbuch der Anatomie der Sinnesorgane, Erlangen, E. Besold, 1887.

21. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage: Its Relation to Preexisting Cerebral Softening, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

22. Sachs, B., in discussion on Craig, W. M., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage, Arch. Neurol. & Psychiat. **35**:701 (April) 1936.

23. Harris, in discussion on Russell, A. E., and Sargent, P.: Apoplectiform Cerebral Haemorrhage: Operation; Evacuation of Blood; Slow Improvement, Proc. Roy. Soc. Med. (Neurol. Sect.) **2**:44, 1909.

24. Penfield, W.: Operative Treatment of Spontaneous Intracerebral Hemorrhage, Canad. M. A. J. **28**:369, 1933.

25. Craig, W. M., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage, Arch. Neurol. & Psychiat. **35**:701 (April) 1936.

26. Stough, J. T.: Choking of the Optic Disks in Diseases Other Than Tumor of the Brain, Arch. Ophth. **8**:821 (Dec.) 1932.

brain, and in 1 of these ventricular puncture was performed to decide the question. The presence of pronounced degrees of papilledema in association with acute cerebral symptoms added to the difficulty in establishing the diagnosis. The case history of 1 of these patients is discussed in detail. It was possible in this case to observe the rapid development of papilledema and retinal hemorrhages during the course of active cerebral hemorrhage, and the ultimate regression of all changes in the fundus as the bleeding stopped and the disturbed intracranial pressure returned to a normal level. A tabular summary of this and the other 22 cases is presented, and the entire series is analyzed with reference to the incidence of ocular changes and the factors responsible for their occurrence.

REPORT OF A CASE

A woman aged 46 (case 22), who had been in previous good health, suffered sudden loss of consciousness at 8 a. m. on Jan. 11, 1937. She was seen by a physician within thirty minutes, when she exhibited transient weakness of the right side of the face and left hemiplegia. Neurologic examination, made one and a half hours after the onset, revealed that the patient was completely unconscious and in a state of violent motor excitement, thrashing the right arm and leg about and shrieking in a loud, shrill voice. The left half of the body, including the left half of the face, was completely paralyzed and flaccid. The pupils were widely dilated and responded sluggishly to light. They had previously been pinpoint in character; it was observed that the size of the pupils fluctuated from time to time. Both eyes deviated to the right. Venous engorgement without retinal hemorrhages and without alteration in the character of the optic disk was observed in the left fundus. The right fundus, on the other hand, contained numerous small, fresh hemorrhages in the vicinity of the retinal veins, which themselves were markedly engorged. The right optic disk was blurred at its nasal margin, while the temporal border was still sharply defined. Examination otherwise revealed little of importance. The deep tendon reflexes on the left were diminished; those on the right were physiologic; the plantar reflexes at this time were unchanged.

Systemic examination gave normal results. The heart tones were normal. The level of the blood pressure fluctuated widely, ranging from 190 systolic and 120 diastolic to 140 systolic and 90 diastolic. The blood chemical findings were within normal limits. Later in the day electrocardiographic tracings characteristic of coronary thrombosis were obtained.

Course.—At 5 p. m. on the first day of illness the right fundus showed a definite increase in the degree of swelling of the disk and in the number of retinal hemorrhages, while the left fundus remained relatively unchanged. Twenty-four hours after the onset of the illness the patient was stuporous and restless; moderate recovery of motor function of the left leg had appeared. The left arm remained paralyzed; the tendon reflexes on the affected side were still depressed; a positive Babinski sign had appeared on the left. At this time the swelling of

Tabular Summary of Twenty-Three Cases of Cerebral Hemorrhage with Papillary Swelling and Retinal Bleeding

Case No.	Patient	Age, Yr.	Sex	Duration of Symptoms	Blood Pressure, Mm. Mercury	Serologic Reactions	Spinal Fluid	Clinical Findings	Ophthalmoscopic Examination: Time of Examination After Onset	Ophthalmoscopic Examination: Arteriosclerosis	Ophthalmoscopic Examination: Papilledema	Ophthalmoscopic Examination: Retinal Hemorrhage	Extent of Hemorrhage in the Brain as Determined at Autopsy: Cerebrum	Cerebellum	Pons	Ventricles	Subarachnoid Space
								GROUP I. CEREBRAL HEMORRHAGE									
								(*a*) Extending into Ventricular System									
1	C. H.	29	M	13 hr.	90/50 to 158/ 70	Negative	Bloody; xanthrochromic; crenation of red blood cells	Sudden loss of consciousness; flaccid paralysis of all extremities; blood sugar 204 mg. per 100 cc.	1 hr. 12 hr.	0	Right +; left — Right +++; left +	0	+	0	0	+	0
2	W. K.	52	M	6 hr.	190/100	Negative	Not examined	Vertigo followed by collapse; flaccid extremities, more on left	6 hr.	+	++	0	+	0	0	+	0
3	F. P.	41	M	14 hr.	105/ 70	Negative	Bloody; 305 mg. protein per 100 cc.	Sudden collapse with loss of consciousness; spasticity and clonic convulsions; no hemiplegia	1 hr. 12 hr.	0	0 Right —; left +	0	+	0	0	+	0
4	A. S.	43	M	4 days	170/100	Negative	Bloody; under increased pressure	Stupor; vomiting; flaccid paralysis of right arm and leg	24 hr.	0	+	0	+	0	0	+	0
5	J. K.	49	M	5 days	210/135	Negative	Bloody; xanthrochromic; under increased pressure; crenation of 50 per cent of red blood cells	Collapse; aphasia, then stupor; flaccid paralysis of right arm; spasticity of right leg	12 hr.	+++	++	0	+	0	0	+	0
								(*b*) Extending into Ventricles and Pons									
6	M. K.	48	F	9 days	100/ 70	Negative	First day: bloody without crenation of red blood cells; subsequently bloody and xanthrochromic	Sudden onset of vomiting, nausea, pain in left eye and abdomen; stupor; partial paralysis of right pupil; right facial weakness; rigid neck; bilateral Babinski sign; sudden death 9 days after onset	1 hr. 48 hr.	0	0 ++	0 Right +++; left +	+	0	+	+	0
7	M. H.	49	F	12 days	265/150	Negative	Pressure increased; grossly bloody; slight degree of crenation of red blood cells	Sudden loss of consciousness without premonitory sign; neck rigid; peripheral facial paralysis on left; alternating flaccidity and rigidity of upper and lower extremities; abnormal plantar reflexes bilaterally	12 hr.	0	++	++	+	0	+	+	0
8	B. B.	57	M	2 days	235/150	Negative	Under increased pressure; bloody; crenated red blood cells	Stupor; vomiting; flaccid paralysis of right arm and leg	48 hr.	+++	++	0	+	0	+	+	0
9	J. C.	47	M	4½ hr.	160/ 90	4+	Bloody, without crenation of red blood cells or xanthrochromia	Coma; left hemiplegia	4½ hr.	++	Right +	Left +	+	0	+	+	0

8	B. B.	57	M	2 days	235/150	Negative	Under increased pressure; bloody; crenated red blood cells	Stupor; vomiting; flaccid paralysis of right arm and leg	48 hr.	+++	++	0	+	0	+	+	0
9	J. C.	47	M	4½ hr.	160/ 90	4+	Bloody, without crenation of red blood cells or xanthrochromia	Coma; left hemiplegia	4½ hr.	++	Right +	Left +	+	0	+	+	0
							(c) Extending to Ventricular System and Subarachnoid Space										
10	L. B.	63	F	3 hr.	220/120	Negative	Under slightly increased pressure; blood-tinged; crenation of red blood cells	Vertigo; vomiting; coma; flaccid paralysis on right with decrease of reflexes	3 hr.	++	++	0	+	0	0	+	+
							(d) Extending to Subarachnoid Space Only										
11	C. A.	63	F	6 days	160/ 95	Kahn reaction of blood and spinal fluid 4+; Wassermann 4+	Grossly bloody and under increased pressure	Stupor; rigid neck; deep reflexes hyperactive but equal; Babinski, Chaddock, Gordon and Oppenheim signs on right	24 hr.	+	+	++	+	0	0	0	+
12	L. G.	63	F	6½ hr.	212/ 60	Negative	Frank blood; crenation of red blood cells and xanthrocromia	Coma; spasticity of all extremities	6 hr.	++	++	++	+	0	0	0	+
							(e) Extending to Pons										
13	A. P.	50	F	2 hr.	High	Negative	Not examined	Headache; visual disturbance; sudden coma; flaccid extremities	2 hr.	+	0	Right ++; left —	+	0	+	0	0
							GROUP II. CEREBELLAR HEMORRHAGE										
							Extending to Ventricles and Subarachnoid Space										
14	J. C.	36	M	1-2 hr.	.....	Negative	Grossly bloody	Dull frontal headache; onset sudden; marked pain in back of neck; rigidity; coma; all reflexes lost; extremities flaccid	1 hr.	0	0	++	0	+	0	+	+
15	J. M.	55	M	6 hr.	140/ 75	Negative	Bloody; under increased pressure, no xanthrochromia; slight crenation of red blood cells	Coma; spasticity of all extremities	6 hr.	—	+	0	0	+	0	+	+
							GROUP III. PONTILE HEMORRHAGE										
							(a) Hemorrhage Limited to Pons										
16	J. W.	44	M	4 days	270/186	Kahn and Wassermann reaction of blood and spinal fluid 4+	.....	Left hemiparesis without loss of consciousness and with spasticity; no aphasia; right hemianopia and hemihypesthesia; sudden coma before death	24 hr.	+++	+++	+	0	0	+	0	0

Tabular Summary of Twenty-Three Cases of Cerebral Hemorrhage with Papillary Swelling and Retinal Bleeding—Continued

Case No.	Patient	Age, Yr.	Sex	Duration of Symptoms	Blood Pressure, Mm. Mercury	Serologic Reactions	Spinal Fluid	Clinical Findings	Ophthalmoscopic Examination: Time of Examination After Onset	Ophthalmoscopic Examination: Arteriosclerosis	Ophthalmoscopic Examination: Papilledema	Ophthalmoscopic Examination: Retinal Hemorrhage	Extent of Hemorrhage in the Brain as Determined at Autopsy: Cerebrum	Cerebellum	Pons	Ventricles	Subarachnoid Space
								(*b*) Hemorrhage Extending to Ventricles and Subarachnoid Space									
17	A. I.	52	M	24 hr.	Elevated	Negative	Bloody	Unconsciousness; flaccidity; severe pain over frontal portion of head and left eye; patient had been treated for heart trouble	24 hr.	—	++	+	0	0	+	+	+
								GROUP IV. SITE OF HEMORRHAGE NOT PATHOLOGICALLY ESTABLISHED									
								(*a*) Ventricular Hemorrhage Clinically									
18	R. D.	61	F	80 hr.	280/?	Negative	Bloody	Headaches; vomiting; aphasia; coma; spasticity of left side, with convulsive seizures	24 hr. 48 hr.	0	+ Right +++; left +	++ +	No autopsy				
19	M. Z.	44	F	8 days	240/120	Negative	Xanthrochromic; cloudy; pressure 160 mm. of water	Coma and bradycardia; flaccid paralysis of left side; bilateral abnormal plantar reflexes	Onset 4 days	0	Right ++++; left 0 Right ++; left +	0 Right +; left 0	No autopsy				
20	I. W.	54	M	12 hr.	120/ 90 230/110	Negative	Not examined	Coma; left hemiplegia	12 hr.	+++	+	0	No autopsy				
21	P. W.	Old	M	24 hr.	100/120	Negative	Bloody	Coma; general flaccidity; reflexes sluggish	24 hr.	—	0	+++	No autopsy				
22	M. A.	46	F	4 mo.	220/120 160/ 80	Negative	Xanthrochromic; bloody	Coma; left hemiparesis; long phychosis before recovery	2 hr. 10 hr.	0	Right +; left — Right +++; left +	Right ++; left — Right ++++; left +	Recovered				
								(*b*) Clinically, Subarachnoid Hemorrhage									
23	P. B.	18	M	1 mo.	110/ 70	Negative	Bloody and xanthrochromic	Headache; meningeal irritation; thrombocytopenic purpura; recovery after splenectomy	24 hr. 6 days 10 days	0	0 + ++++	0 + ++++	Recovered				

the right disk was pronounced, involving all borders; new hemorrhages were scattered in the retina. In the left fundus a slight degree of blurring had appeared in the nerve head, and one small hemorrhage was seen near the temporal border of the disk. Within the following twelve hours there developed stiffness of the neck, a positive Kernig sign and obvious symptoms of meningeal involvement.

The question of diagnosis was presented. The onset and course were strongly in favor of a cerebral vascular lesion, hemorrhagic in type and subcortical or cortical in origin. The progressive ocular findings, however, presented the problem of tumor of the brain and the question of the advisability of or contraindication to spinal puncture. Ventricular injection of air was considered to be the procedure of choice.

The operation was performed at 1:50 a. m. on January 13. Fifty cubic centimeters of bloody fluid was removed from the left ventricle. Ventriculograms demonstrated bilateral dilatation of the ventricles, with practically no distortion and with the septum pellucidum in the midline. These observations supported a diagnosis of cerebral hemorrhage with ventricular rupture.

During the subsequent six days the patient remained comatose. Motion in the paralyzed extremities gradually returned, the motor power increasing daily. The deep tendon reflexes on the left were completely abolished, as were the abdominal reflexes on both sides. The left plantar reflex was extensor in type. Rigidity of the neck and a Kernig sign persisted. During this period the blood pressure fluctuated erratically and widely, reaching a systolic pressure of 220 mm. of mercury. Electrocardiograms persistently showed signs characteristic of coronary thrombosis, although at no time did the patient exhibit any clinical symptoms or cardiac signs of myocardial disturbance. With the return of consciousness the patient showed left homonymous hemianopia and intensification of preexisting deafness. The left sixth cranial nerve was paralyzed. Spontaneous nystagmus appeared. This was followed on January 23 by right oculomotor paralysis. By January 21 decrease in the swelling of the optic nerves and absorption of the retinal hemorrhages had begun.

On January 24 manic symptoms appeared and progressed to a characteristic manic type of psychosis. Although the patient recognized and identified people about her, she was disoriented, confused, delirious and totally without judgment and insight. She became noisy and combative. The paralysis had improved so that she was now ambulatory. Neurologic examination showed signs characteristic of hemiplegia; apparently, all active bleeding had stopped. The psychosis became the outstanding problem. For three weeks the patient was out of touch with her environment. When she finally recovered orientation, in the middle of March 1937, she was completely amnesic for events up to that time. In the following months rapid progress, both physical and mental, was made. In June 1937 she still exhibited faulty judgment; residuals of hemiplegia were minimal. The reflexes were normal. The ocular fundi were completely normal, and vision was the same as it had been prior to the onset of the illness.

COMMENT

Before discussion of the significance of clinical and pathologic details of the cases studied, it seemed well to refer to present conceptions of the mechanism of formation of papilledema. Lauber [27] has reviewed the theories. Various factors have been blamed: the effect of increased intracranial pressure on the production of venous and lymphatic stasis; extension of cerebral edema to the optic nerve and disk; elaboration of toxins from a tumor of the brain, with resultant inflammation of the disk, and vascular irritation, on a nerve basis.

The theory of lymphatic and venous stasis has received the most consideration. All others merit little support. Von Graefe [28] and Türck [28] expressed the belief that high intracranial pressure acts by compressing the cavernous sinus, thereby obstructing venous outflow from the eye. Seseman [28] demonstrated the presence of venous collaterals which make such a sequence of events improbable, while Marckwort [28] asserted that ischemia, rather than congestion, follows ligation or compression of the optic nerve. Subsequently, the studies of Sobański [29] established that compression of the central retinal vein alone, without involvement of the arterial circulation, results in papilledema; obstruction of the artery by direct ligation produced the result recorded by Marckwort.

Many authorities have claimed that venous obstruction occurs at the site of exit of the central retinal vein from the optic nerve or in its course through the intervaginal sheaths of the optic nerve. Paton and Holmes [30] verified this in anatomic studies on 60 cases of tumor of the brain. They examined histologically the disks and optic nerves; they described papilledema as simple edema of the extracranial portion of the optic nerve and the optic disk. The nerve proximal to the exit of the central retinal vein was unaffected. Vascular congestion was the earliest sign of papilledema, resulting first in hyperemia of the disk and later in dilatation of the smaller vessels. Hemorrhages occurred ultimately. The authors claimed that these were the best evidence of congestion. The central retinal vein was dilated in the disk and in the optic nerve as far back as its exit into the sheath. In a few cases the subarachnoid space of the nerve sheath contained small hemorrhages. The vein usually appeared to be collapsed as it traversed the spaces of

27. Lauber, H.: Die Entstehung der Stauungspapillae, Wien. klin. Wchnschr. **47**:1537, 1934; Formation of Papilledema, Arch. Ophth. **13**:733 (May) 1935.

28. Cited by Lauber.[27]

29. Sobański, J.: Der Blutkreislauf in der Netzhaut unter physiologischen Bedingungen, Arch. f. Ophth. **135**:372, 1936; Der Augendruck und sein Einfluss auf den Blutkreislauf in der Netzhaut, ibid. **135**:383, 1936.

30. Paton, L., and Holmes, G.: Pathology of Papilledema, Tr. Ophth. Soc. U. Kingdom **31**:117, 1911.

the sheath. Paton and Holmes concluded that elevations of intracranial pressure are transmitted to the spaces of the optic nerve sheath, directly compressing the veins which cross them. This results in venous stasis. In the opinion of these authors, lymph flow, in like manner, is obstructed, followed by swelling of the disk.

The sheaths of the optic nerve were described by Schwalbe as continuations of the meninges of the brain. The subdural and subarachnoid spaces surrounding the optic nerve communicate posteriorly with the meningeal spaces of the brain and terminate anteriorly as cul-de-sacs on the eyeball. The mechanism whereby alterations in intracranial pressure affect the retinal vein has been discussed. That direct effects of pressure on the optic nerve may occur has been maintained by Schmidt, Rimpler and Manx,[28] and others have claimed that the pressure effect produces dilatation of the perivascular lymphatic vessels, interfering with circulation of lymph from the eyeball to the cranial cavity. Behr [28] considered the possibility of obstruction of lymph flow into the intervaginal sheaths. He contended that this stasis of lymph accounts for papilledema.

The use of the ophthalmodynameter of Bailliart,[28] Baurmann [31] and Sobański [29] has contributed much information on the relation between intracranial pressure and the intraocular and retinal vascular pressures. Whenever the intraocular pressure equals the pressure in the retinal veins pulsation occurs in the veins. This furnishes one means of measuring the retinal venous pressure. Lauber determined that the average retinal venous pressure increases with age under normal conditions. In addition, there exists a normal relation between the level of the retinal venous and the retinal arterial pressure. This ratio has been established by Lauber to range from 1:1.9 to 1:1.3. Furthermore, there appears to be a definite relation between systemic and retinal arterial pressure. Bailliart expressed this relation by the formula: retinal diastolic pressure: brachial diastolic pressure = 45:100.

There is conflicting opinion as to the effect of changes in intracranial pressure on retinal vascular pressures. Bailliart expressed the belief that alterations in the intracranial pressure are reflected directly in the level of the retinal diastolic pressure. If retinal diastolic pressure exceeded half the brachial diastolic pressure, in the absence of local causes in the retina, the change was ascribed by him to elevations of intracranial pressure. Bailliart did not accept alterations in retinal venous pressure as a reliable index of fluctuations of pressure within the cranial cavity. This view is opposed to that of Baurmann and his followers, who insisted that retinal venous pressure is a constant and

31. Baurmann, M.: Vergleichende Blutdruckmessungen an den Gefässen des Auges, Arch. f. Ophth. **118**:118, 1927; Ueber die Schwankungen des intrakraniellen Druckes, ibid. **129**:205, 1932.

equivalent index to the level of the spinal fluid pressure, whereas increases in retinal arterial pressure reflect merely concomitant alterations in systemic blood pressure. Gibbs [32] recently confirmed Baurmann's observations.

Lauber, in a study of 93 patients, analyzed the effects on spinal fluid pressure of alterations in the systemic blood pressure and retinal vascular pressure and their relation to the development of choked disk. He came to the conclusion that the retinal venous pressure can be used as an index to the spinal fluid pressure, with which it stands in direct relation. By estimating the level of pressure at which pulsations appeared in retinal veins, Lauber found that he could estimate spinal fluid pressure with only a slight degree of error, which becomes smaller when spinal fluid pressures are high. Kukán,[33] agreeing with the principle that retinal venous pressure is a reflection of spinal fluid pressure levels, pointed out that corrections in estimations by this method must consider the effects of intraocular tension on retinal vascular pressure. The entire ocular vascular system has a higher pressure than similar vessels in other parts of the body. Kukán contended that proper allowance must be made for these differences.

In the opinion of Lauber, the development of papilledema in cases of elevated intracranial pressure is dependent on the respective levels of retinal venous and retinal arterial pressure. When the retinal arterial pressure is low a slight change in retinal venous pressure produces venous congestion and papilledema; venous pressure of from 20 to 30 mm. of mercury produces hyperemia; pressure of 35 mm. of mercury results in well defined papilledema. On the other hand, in the presence of high retinal arterial pressure a higher venous pressure is required to produce comparable results: A venous pressure of 35 mm. of mercury produces no change in the disk; a pressure from 40 to 45 mm. of mercury results in hyperemia, whereas higher venous pressures are required to produce choked disk. Lauber stated the relationship between retinal vascular pressures and their effect on the optic nerve disk as follows: When the ratio between retinal venous and retinal arterial pressure ranges from 1 : 1.7 to 1 : 2.6 no changes in the disks occur; when the ratio ranges from 1 : 1.7 to 1 : 1.5 the disks become blurred; when the ratio is beyond 1 : 1.5 papilledema always occurs.

Intraocular tension itself adds another factor in the production of papillary changes. In Noiszewski's [33a] experience, very high intraocular

32. Gibbs, F. A.: Relationship Between the Pressure in the Veins on the Nerve Head and the Cerebrospinal Fluid Pressure, Arch. Neurol. & Psychiat. **35**:292 (Feb.) 1936.

33. Kukán, F.: Ueber die Beziehungen des Gefässdruckes der Netzhaut zu dem Hirndruck auf Grund von mit eignem Gerät angestellten Untersuchungen, Klin. Monatsbl. f. Augenh. **97**:331, 1936.

33a. Cited by Lauber.[27]

tension has resulted in backward displacement of the cribriform plate when the intraocular tension exceeded the intracranial tension. On the other hand, Paton and Holmes and others observed how much more rapidly papilledema occurs when intraocular tension is low; when the intraocular tension of the two eyes differs, papilledema invariably occurs in the eye with the lower tension.

The mechanisms responsible for changes in the fundus in 23 patients studied in the present report are more clearly understood when it is possible to correlate the clinical symptoms and the observations at autopsy with the ophthalmoscopic pictures. Age incidence, arteriosclerosis, syphilis, spinal fluid pressure, blood pressure, duration of symptoms and the extent of the cerebral hemorrhage are factors to be considered.

The ages of the patients ranged from 18 to 63 years; the patients may be divided into groups on the basis of age, as follows: 18 to 40, 3 patients; 41 to 50, 8 patients; 51 to 60, 6 patients, and 61 to 67, 5 patients. The age of 1 patient was unknown. Significant degrees of retinal arteriosclerosis were described in 10 patients, the ages of whom were from 47 to 63. From the meager data available, no relationship was evident between the incidence and degree of retinal arteriosclerosis and the development of the fundic changes. This conclusion is in accord with that of Cohen.[34] The age group characteristic of apoplectic persons falls definitely into that of the arteriosclerotic class, and one might well expect the same percentage of arteriosclerosis found in my series to occur in any group of persons of similar age.

Syphilis is readily dismissed as an etiologic factor in the fundic changes. Only 3 patients had syphilis, as indicated by the Wassermann reaction of the spinal fluid. In none of these, however, was there other clinical evidence of syphilis of the central nervous system, and at autopsy the cerebral vessels and meninges, as well as the parenchyma, failed to show characteristic syphilitic lesions.

Hypertension was present in each patient; the figures recorded in some instances do not necessarily represent the true level of the blood pressure, since shock produced its effect at one time or another. There appeared to be no correlation between the level of either the systolic or the diastolic pressure and the fundic lesions.

The spinal fluid of all but 1 patient (case 16) was bloody. The exception represented the 1 instance in which hemorrhage extended neither to the ventricles nor to the subarachnoid space. Xanthochromia and crenation of red blood cells depend entirely on the age of the hemorrhage, as indicated by successive punctures. They were not present in early punctures, but appeared in the later ones. The spinal fluid pressure in each case was high; unfortunately, manometric readings were not made, and the state of the spinal pressure was estimated only by the force with which the fluid escaped.

Early changes in the fundi are the rule after spontaneous intracranial hemorrhages. Well defined papillary and retinal alterations were present within forty-eight hours in 21 cases. The shortest interval within which fundic changes appeared after the onset of cerebral symptoms was two hours (in 4 cases of papilledema and retinal hemorrhages). There did not appear to be any direct parallelism between the extent of papillary swelling and the severity of the retinal

34. Cohen, M.: Value of Ophthalmoscopic Signs in the Pre-Apoplectic Stage, Psychiatric Quart. **2**:59, 1928.

hemorrhages in any individual fundus. In 1 patient exhibiting papilledema within two hours of his illness, no hemorrhages occurred; on the other hand, another patient, showing hemorrhages early, suffered no papillary changes. Similarly, there was no parallelism in the degree of changes in the two eyes of any one patient. Venous congestion, however, was a constant and early finding in all fundi.

Ocular disturbances appeared within six hours in 7 patients, in from six to twelve hours in 6 patients, in from twelve to twenty-four hours in 7 patients and in from twenty-four to forty-eight hours in 2 patients. One patient (case 23) suffered continuous subarachnoid hemorrhage for many days. Seventy-two hours after his illness began the fundi were still normal. However, as the bleeding continued, blurring of the margins of the disks appeared on the sixth day, and retinal hemorrhages were evident. Marked papilledema with obliteration of the entire disk occurred on the tenth day, together with massive hemorrhages into the retinas. With the cessation of intracranial bleeding abnormalities in the fundus regressed, with considerable improvement in three weeks.

Autopsy in 17 of the 23 cases determined the extent and location of the cerebral hemorrhage. Permission for autopsy was refused in 4 cases. The remaining 2 patients of the series recovered. Cerebral hemorrhage occurred in 13 cases, cerebellar hemorrhage in 2 and pontile hemorrhage in 2. Of the 2 patients who recovered, 1 (case 23) was a youth aged 18 whose subarachnoid hemorrhage was controlled by splenectomy for thrombocytopenic purpura. In the other, a woman aged 46 (case 22), ventricular tap showed considerable blood in both lateral ventricles. She made complete recovery, after a stormy course. In each of these 2 patients it was possible to observe the development of papilledema and retinal hemorrhages early in the course of the illness and to watch the recession of the ocular changes as the bleeding stopped and the hemorrhage was absorbed. In case 23 marked improvement was observed in three weeks; in the other complete restoration to normal appearance of the fundi occurred within three months.

In each of the 4 patients on whom no autopsy was performed the clinical picture was that of intraventricular hemorrhage. However, it was impossible to determine with certainty the primary site of the bleeding or to be sure whether massive bleeding was present in both the ventricular system and the subarachnoid space or in either region without involvement of the other. In 3 of these patients papilledema occurred; in 3 retinal hemorrhages were present. Symptoms of hemmorrhage lasted from twelve hours to eight days.

The 13 cases of proved cerebral hemorrhage may be grouped as follows: 1. Hemorrhage with rupture into the ventricles, 5 cases (nos. 1, 2, 3, 4 and 5). Papillary swelling of various degrees occurred in each case, but retinal hemorrhages were absent in all. Death followed in from six hours to five days after the onset of symptoms. 2. Rupture into the ventricles and extension of the hemorrhage into the pons, 4 cases (nos. 6, 7, 8 and 9). In 2 cases is was possible to trace the extravasation of blood along the pyramidal tracts to the brain stem. Papillary swelling was observed in each case; retinal hemorrhages, in 3 cases. The duration of symptoms was from four and a half hours to nine days. 3. Rupture into the ventricles with extension into the pons and subarachnoid space, 1 case (no. 10). Death occurred within three hours, during which time swelling of the optic disk appeared but retinal hemorrhages failed to materialize. 4. Rupture into the subarachnoid space without involvement of the ventricular system, 2 cases (nos. 11 and 12). Both the patients exhibited papilledema and retinal hemorrhages within six and a half hours after the onset of symptoms. 5. Extension of the cerebral hemorrhage to the pons only, 1 case (no. 13). There was no involvement of the

ventricles or subarachnoid space. This patient died within two and a half hours. The fundi showed normal disks, while retinal hemorrhages were well marked.

Primary cerebellar hemorrhage with rupture into the fourth ventricle and extension into the subarachnoid space occurred in 2 cases. In 1 patient (case 14), who died within two hours, retinal hemorrhages were present, while the disks remained normal. In the second patient (case 15) no retinal bleeding occurred, but swelling of the disks appeared before death occurred, six hours after the stroke.

Primary pontile hemorrhage caused the death of 2 patients. In 1 of these (case 16) no extension of the bleeding beyond the limits of the pons was discovered. Both retinal hemorrhage and papilledema were present. The patient lived for four days after he became ill. In the second patient (case 17) the hemorrhage extended into the ventricles and the subarachnoid space. Here, also, were both retinal hemorrhage and papilledema.

In all, ventricular bleeding was present in 13 of the 17 cases in which autopsy was performed, pontile hemorrhage in 7 and subarachnoid hemorrhage in 6. Ocular changes were present in each of the 23 patients; papilledema was noted in 20, retinal hemorrhage in 14, arteriosclerosis, pronounced enough to be described, in 10. In 7 patients it was possible to observe the development of the changes in the fundus during the course of the disease. Retinal hemorrhages were present in the fundi of 5 of the 7 patients with proved subarachnoid hemorrhage; similarly, 5 of the 7 patients with pontile hemorrhages exhibited retinal bleeding. On the other hand, in 5 patients with intraventricular hemorrhage, without either pontile or subarachnoid hemorrhage, retinal bleeding failed to occur. In only 2 of the entire series was pronounced arteriosclerosis associated with retinal hemorrhages.

These figures indicate that subarachnoid and pontile hemorrhages favor the development of retinal hemorrhages, while with uncomplicated intraventricular hemorrhage papillary swelling without retinal changes occurs. The significance of retinal hemorrhages has already been discussed. They are now generally regarded as evidence of pronounced stasis of the central retinal vein. Bleeding into the subarachnoid space of the optic nerve sheath, a common accompaniment of hemorrhage into the meninges of the brain, may produce mechanical compression of the central retinal vein as it emerges from the optic sheaths, rapidly producing the effects of stasis. This effect would be exerted in addition to the elevation of intervaginal pressure accompanying intracranial rise. Under such conditions, Uhthoff [35] observed the development of retinal hemorrhages within a few hours. It is probable that similar mechanisms explain the frequency of retinal hemorrhages in the cases of subarachnoid hemorrhage under discussion.

Pontile hemorrhage, without subarachnoid extravasation, however, must produce its effect in a more indirect manner. The pathologic conditions are comparable with the development of any sudden increase in the contents of the posterior fossa, with the rapid development of high

35. Uhthoff, W.: Beitrag zur Kenntnis der Sehnervenveränderungen bei Schädelbruchen, speciell des Hämatoms der Sehnerverscheiden, Ber. ü. d. Versamml. d. ophth. Gesellsch. **28**:143, 1901.

intracranial pressure. This pressure, transmitted rapidly to the optic nerve sheaths, produces also a rapid venous stasis, with resultant retinal hemorrhages and papilledema. Analogous circumstances may be found in cases of acute syphilitic meningitis, as described by Moore [36] and Alpers and Yaskin,[37] in which papillary and retinal changes appear with great rapidity. Apparently, syphilitic lesions in the posterior fossa are associated with the development of acute internal hydrocephalus, which may also accompany bleeding into the pons.

With the development of intraventricular hemorrhage there is a progressive increase in intracranial pressure, which inevitably will produce papilledema if the patient lives long enough and if the ocular conditions are favorable for its development. This means, according to the latest thought, a proportionate pressure relationship between the arteries and veins in the retina and the intraocular tension. In most cases of intracranial hemorrhage there is some degree of hypertension which, according to Lauber, acts against the formation of papilledema. Similarly, ocular tension is apt to be relatively high in older persons, further decreasing the tendency to papilledema. In cases in which papilledema occurs the intracranial pressure must reach considerable heights.

The incidence of fundic changes following massive cerebral hemorrhage is certainly higher than is indicated by available statistics. Autopsy was performed in 153 cases of massive cerebral hemorrhage at the City Hospital within a period of three years. In 17 of this group changes were observed in the fundus. Furthermore, the interest of the attending physicians contributed to a large extent in adding to the group of cases in which fundic lesions occurred. When particular attention was paid to the problem thorough ocular examinations were made, with the result that fewer cases of ocular complication escaped attention.

SUMMARY AND CONCLUSION

The ocular fundi in 23 cases of massive hemorrhage of the brain were examined, in 7 on a number of occasions over a period of hours or days. Swelling of the optic disk was found associated most often with intraventricular hemorrhage, which was not accompanied by a subarachnoid or pontile hemorrhage. Retinal hemorrhages were not found to be characteristically associated with retinal arteriosclerosis, but occurred in the course of subarachnoid and pontile hemorrhage.

The appearance of papilledema and retinal hemorrhages in cases of cerebral hemorrhage leads on occasion to difficulties in differentiation from tumor of the brain.

36. Moore, M.: Acute Syphilitic Meningitis, Arch. Neurol. & Psychiat. **32:** 1360 (Dec.) 1934.

37. Alpers, B. J., and Yaskin, J. C.: Choked Disc in Syphilis of the Nervous System, Am. J. M. Sc. **190:**333, 1935.

CEREBRAL CHANGES IN FATAL CASES FOLLOWING TREATMENT WITH BARBITAL, SOLUBLE BARBITAL U. S. P., INSULIN AND METRAZOL

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Attempts to treat some mental disorders (schizophrenia; manic-depressive conditions) with methods inducing prolonged sleep, insulin shock and convulsions bring up the question whether such methods cause morphologic cerebral changes which can be held responsible for the remarkable clinical effects. The results of action on the brain of barbiturates, insulinism and metrazol have been studied in a few patients with pathologic conditions, but those of hyperinsulinism and metrazol have been studied more extensively on animals.[1]

The present report pertains to a study of changes in the central nervous system of 5 patients who died of poisoning with barbital (2 cases), poisoning with soluble barbital U. S. P. (1 case) and shock induced with insulin or metrazol (1 case each). Pyroxylin and frozen sections were used.

REPORT OF CASES

CASE 1.—*Barbital poisoning.*

A World War veteran was found, on Aug. 31, 1929, in a semicomatous condition, with three empty bottles which had contained barbital tablets in a wastebasket by his bed. No information was obtained as to the size of the bottles or tablets or the time the victim had spent at the place where he was discovered. He was removed

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1. Stief, A., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434, 1932. von Meduna, L.: Ueber experimentelle Campherepilepsie, Arch. f. Psychiat. **102**:333, 1934. Grayzel, D. M.: Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694 (Nov.) 1934. Stender, A.: Ueber Provokation epileptiformer Anfälle durch Cardiazol, München. med. Wchnschr. **84**:1893, 1937. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190 (Feb.) 1937. Reitman, F.: Zur Frage der zerebralen Veränderungen bei experimentellen Cardiazolvergiftungen, Psychiat.-neurol. Wchnschr. **40**:391, 1938. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

to the Veterans Administration Facility, Hines, Ill., where he died two days later. Necropsy was performed by the coroner's physician, who observed traces of barbital in the liver and kidneys.

The brain was delivered to my laboratory, in a solution of formaldehyde, about eight weeks after the necropsy. It had already been cut into numerous slabs; so a proper macroscopic description cannot be given.

Microscopic Observations.—The subarachnoid space was distended, especially around the cerebellum, and the pia-arachnoid was densely infiltrated with lymphocytes, polyblasts and fibroblasts. The parenchyma of the medulla, pons and optic thalamus appeared edematous, and a large hemorrhage was present in the medulla, near the floor of the fourth ventricle, with numerous microgliocytes containing granules of blood pigment. The ganglion cells and their processes, especially in deep layers of the cerebral cortex, and the Purkinje cells were swollen; those of the medulla oblongata, chiefly the large cells of the nucleus of the twelfth nerve, showed no changes, while the ganglion cells of the olives were expanded by excessive amounts of yellow-green pigment in the cytoplasm (fig. 1*A*). Signs of satellitosis and neuronophagia were not in evidence, nor were there in the cortex or brain stem signs of microglial, astrocytic or oligodendroglial reaction. No neurofibrillary changes or excessive accumulations of lipoids were observed.

Aside from the medullary hemorrhage, the outstanding pathologic features in this case of barbital poisoning were widespread swelling or tumefaction of the ganglion cells, for the most part in the olivary bodies, with a marked reaction in the meninges (aseptic meningitis) and without microglial or neuroglial reaction of satellitosis and neuronophagia. The pathologic condition may be classified as acute cell disease of Nissl, combined with aseptic meningitis and mild edema of the brain.

CASE 2.—*Barbital poisoning.*

A white woman aged 40 who, according to the history, suffered from a parkinsonian state, was admitted to the Cook County Hospital in a comatose condition and died there two days later. According to the husband, the patient had taken 50 tablets of barbital two days previously. The outstanding changes in this, as in the previous, case were: distention of the pia-arachnoid (fig. 2), which was infiltrated with lymphocytes, polyblasts and fibroblasts; rarefaction of the parenchyma of the brain, the medulla and especially the pons, and tumefaction of the ganglion cells throughout the brain, including those of the basal ganglia and cerebellum. The processes of these cells were tortuous, and the nuclei were pale, disfigured and poor in chromatin, which was frequently dustlike. The ganglion cells of the medullary olives not only were swollen and distended with a yellow-green pigment but were also homogeneous; their nuclei showed no changes; the microglia was not conspicuous, and the oligodendroglia was densely stained (pyknotic). The blood vessels were congested, but exhibited no changes in the walls. The tuft cells of the choroid plexus contained numerous chromatin granules at the periphery.

Hemorrhages in this case were absent, but the changes, as in the previous case, were those of acute cell disease of Nissl and, again, were striking in the olivary bodies of the medulla.

Somewhat more advanced were the cerebral changes in a case of death from soluble barbital.

CASE 3.—*Death from soluble barbital.*

A woman aged 29, suffering from schizophrenia, received at the Psychiatric Institute of the University of Illinois within three months sixty-two injections of sodium amytal. As there was little, if any, improvement, *Dauerschlaf* was induced with soluble barbital, of which 120 grains (7.8 Gm.) was given in the

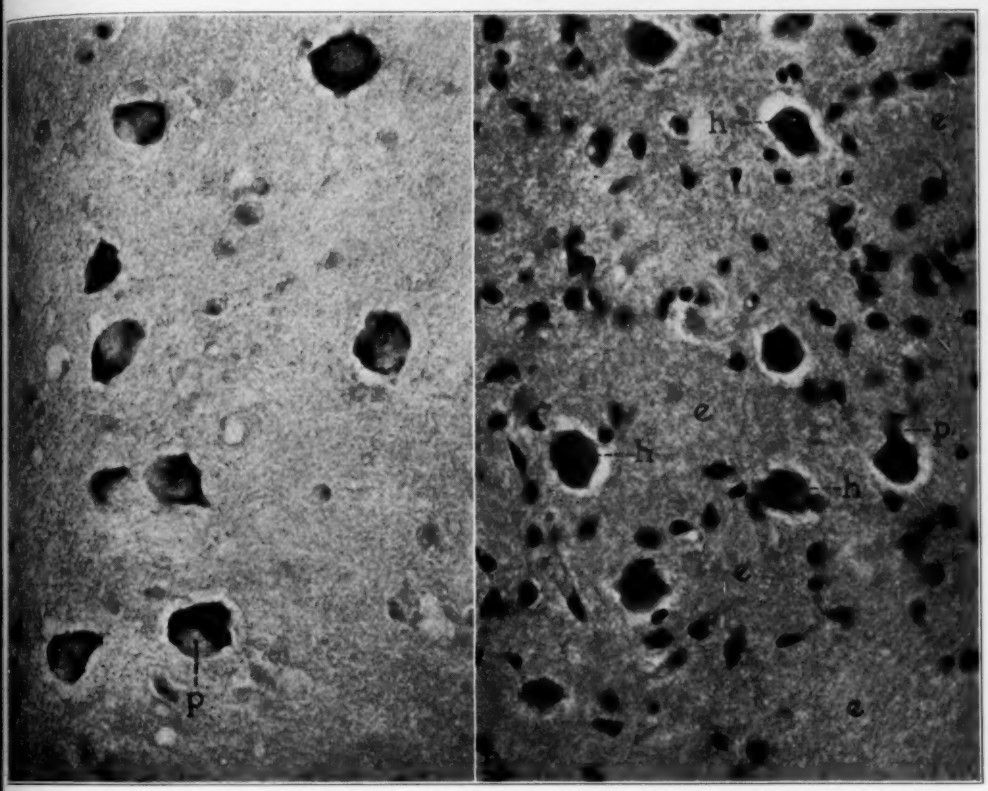

Fig. 1.—*A* (case 1), barbital poisoning. The ganglion cells of the medullary olives are expanded by vast accumulation of pigment (*p*), which occupies almost the entire cytoplasm.

B (case 3), soluble barbital poisoning. The ganglion cells (*h*) of the olivary bodies of the medulla oblongata are homogeneous and expanded and show pigment (*p*); the dendrites are swollen and missing in many cells; the parenchyma (*e*) is edematous and rarefied. Toluidine blue stain; × 400.

first twenty-four hours and 55 grains (3.58 Gm.) in the second twenty-four hours. After the second twenty-four hours the patient became restless and went into a deep sleep, which was followed two days later by a temperature of 104 F., coma and death. The terminal temperature was 107.6 F.

Macroscopic Observations.—Nothing pathologic was observed except for engorged veins of the pia.

Microscopic Observations.—The subarachnoid space around the cerebellum and the convexity of the brain showed marked reactive phenomena—histiocytes filled with pigment granules and fibroblasts mixed with red blood cells; changes in the

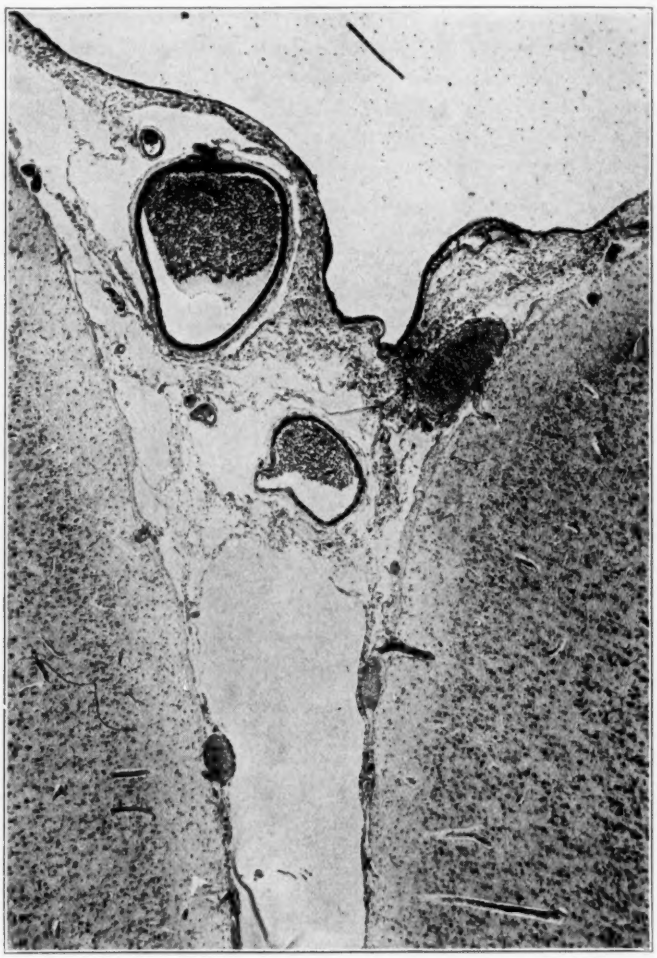

Fig. 2 (case 2).—Parieto-occipital area in a case of barbital poisoning. The subarachnoid space is dilated and densely infiltrated, especially in the right half; the pial veins lodged within the distended meshes of the pia-arachnoid are hyperemic and are not infiltrated.

ganglion cells were in evidence throughout, especially in the medulla, basal ganglia and pons. In the olives, for instance, the ganglion cells were pale and homogeneous (fig. 1 *B*); their nuclei were irregular in shape and poor in chromatin, which was often represented by a few densely stained granules. Other cells in the medulla

were less swollen and occasionally were shrunken, but exhibited chromatolysis and contained an abundance of greenish pigment. In the pons, and partly in the medulla, some ganglion cells were devoid of Nissl bodies; others were liquefied, and their nuclei were broken up or dissolved. In the corpus striatum the majority of the ganglion cells, especially the large ones, were swollen (fig. 3 *A* and *B*); many were liquefied and exhibited phenomena of neuronophagia. The subcortical white matter was rarefied and edematous and contained swollen oligodendroglia cells and numerous microgliocytes. The adventitial cells of the blood vessels harbored much

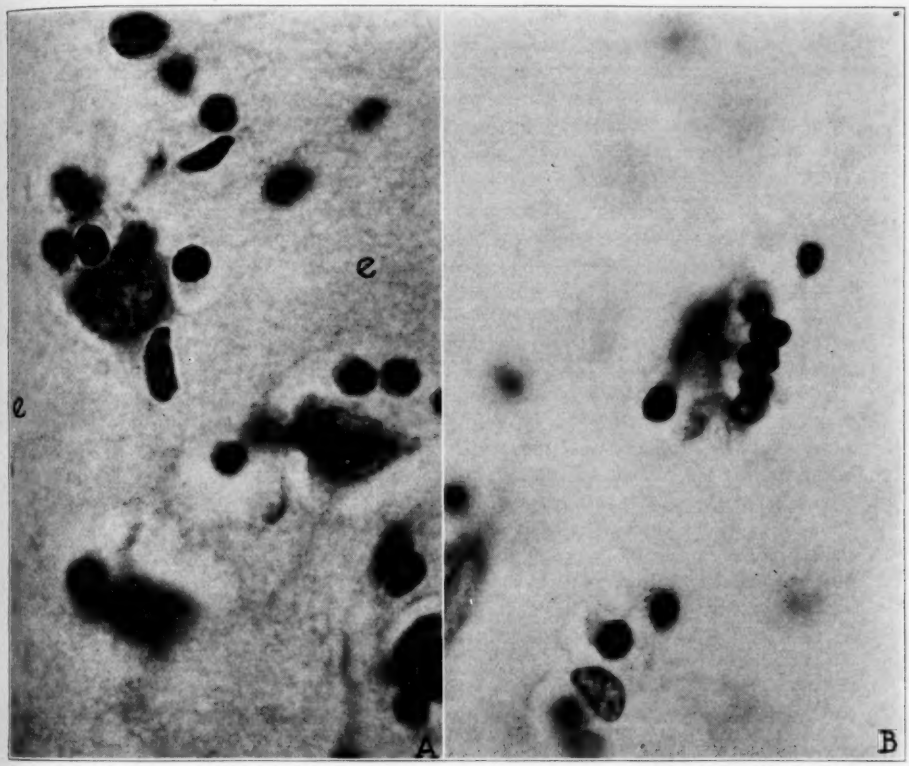

Fig. 3 (case 3).—Soluble barbital poisoning. *A*, edematous parenchyma is indicated by *e*. Swollen ganglion cells are surrounded and almost invaded by neuronophages.

B, in the center a liquefied ganglion cell is invaded by several neuronophages. Toluidine blue stain; × 1,000.

green pigment. Lipoids were present in moderate amounts in the ganglion cells of the cortex and brain stem.

The changes were similar to those described in the preceding 2 cases, but were more diffuse and advanced. In short, they were more extensive and intensive. As in the previous 2 cases, there were signs of cerebral

edema without signs of transformation of microglia cells into fat granule bodies. Nor was there any neuroglial reaction to changes in the blood vessels or capillaries. The difference in the pathologic picture in case 3 may be due to the fact that large doses of the drug were administered after prolonged treatment with sodium amytal.

Even more marked were the changes in a case of death from insulin shock.

CASE 4.—*Insulin shock.*

A white woman aged 51 had been treated at the Psychiatric Institute of the University of Illinois with prolonged sleep (in March 1937); artificial fever (ten treatments of typhoid vaccine in April and May); injections of metrazol (twenty-six treatments, with thirteen paroxysms), after which there were mild improvement and a relapse, and insulin (in November). She had seven insulin treatments (the largest dose being 40 units), with five comas, all of which were interrupted after one hour by feeding of a solution of sucrose by tube. The patient died on Dec. 8, 1937, of pneumonia, which resulted from a tube feeding.

Microscopic Observations.—There were: marked distention of the subarachnoid cerebral space with reactive meningeal elements—lymphocytes, foci of mesothelial cells, polyblasts and fibroblasts—edema of the cerebral parenchyma; swelling of the ganglion cells and their dendrites throughout the brain and basal ganglia, with occasionally marked neuronophagic phenomena; lipoids within the ganglion cells and the adventitial spaces of the blood vessels, and shrinkage, rents (fig. 4) or fissures in the parenchyma in numerous regions—the motor area, optic thalamus and cornu ammonis. In the rents of the optic thalamus remnants of the brain tissue could be discerned, and the oligodendrocytes along the margins of the rent contained scattered, densely stained chromatin granules exhibiting karyorrhexis. The cells of the olivary bodies, which were stained with the Bielschowsky stain, showed, as in the other 3 cases, swelling of the cell bodies with accumulation of dark granules, evidently pigment, around the nuclei, which were expanded. The blood vessels were congested, and the adventitia of their walls occasionally showed signs of proliferation.

The outstanding feature in this case was edema of the cerebral parenchyma, though in the main pathologic features this case resembled the 3 previous cases. The changes were more advanced as the duration of the treatment was longer (ten months), from March 25 to December 8.

CASE 5.—*Death from metrazol.*

A white woman who had been treated with metrazol at the St. Francis Hospital, Peoria, Ill., died in shock shortly after a metrazol convulsion. Dr. A. Bohrod, who performed the autopsy, informed me that the patient received insulin therapy six days a week from Jan. 19 until Feb. 3, 1938. On February 7 she was given 4 cc. of a 10 per cent solution of metrazol, but had no convulsion. On February 8 she received 5 cc. of metrazol and had a convulsion; shortly after she went into shock, from which she did not recover.

Macroscopic Observations.—The convolutions were narrow; the sulci were deep; the meninges were transparent; no changes were present at the base of the brain.

Microscopic Observations.—There were: dilation of the subarachnoid space, which contained a few histiocytes; slight swelling of many cortical ganglion cells and their processes; severe changes in the corpora quadrigemina and basal ganglia, where both the large and the small ganglion cells exhibited marked swelling and abundance of lipoids in the cytoplasm; a normal condition of the ganglion cells of the occipital lobe and the motor area, but marked changes in the pons and

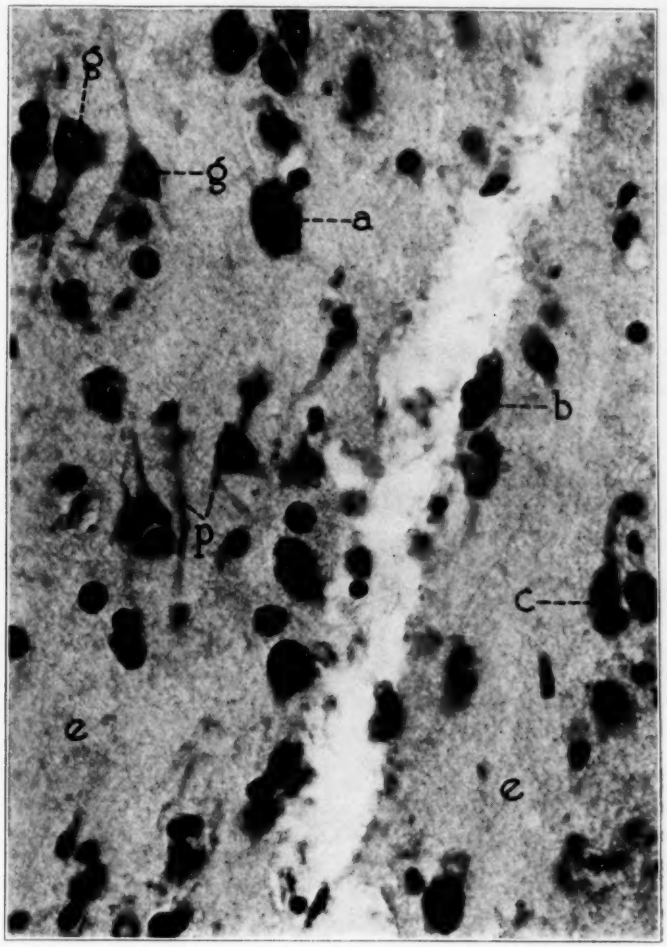

Fig. 4 (case 4).—Death from insulin. Edema of the parenchyma, with rarefaction of tissues, is shown at *e;* swelling of the ganglion cells, especially of their processes at *g*; neuronophagia at *a, b* and *c,* most marked at the margin of the rent in the center of the picture, and swollen processes at *p*. Toluidine blue stain.

medulla (fig. 5), where the ganglion cells, especially of the olivary bodies, not only were swollen but exhibited chromatolysis, abundance of pigment and occasional neuronophagia and numerous microglia cells, which were mixed with swollen

oligodendrogliocytes. Edema of the parenchyma of the cornu ammonis was in evidence; the tuft cells of the choroid plexus were vacuolated, and their nuclei were densely stained and disfigured; some cells contained numerous marginal granules. No changes were present in the blood vessels or neuroglia.

In short, swelling of the ganglion cells, chromatolysis and occasional edema, liquefaction and neuronophagia were the outstanding pathologic features in this case. It is possible that the histologic changes may have been influenced by the previous insulin treatment. In a case of Hayman and Brody,[2] in which sudden death occurred after six treatments with metrazol, no changes were seen in the meninges, blood vessels or individual nerve cells.

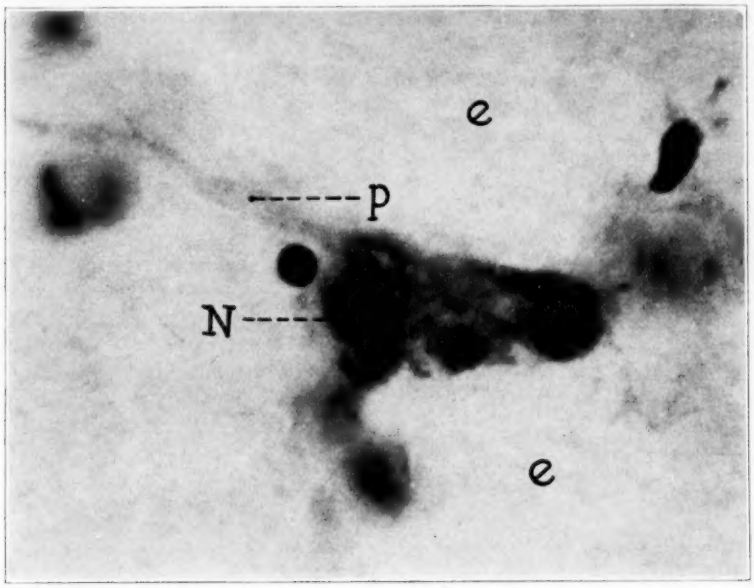

Fig. 5 (case 5).—Death from metrazol. A typical instance of so-called severe cell disease of Nissl. Edema of the tissues is indicated by *e*. In the center are a ganglion cell and its process (*p*); both are swollen, almost liquefied and invaded by a neuronophage (*N*). Toluidine blue stain; × 1,400.

GENERAL COMMENT

In the 5 cases recorded here, the main morphologic features in common were: aseptic meningitis with dilatation of the subarachnoid space; edematous condition of the parenchyma; diffuse changes in the ganglion cells, in the form of tumefaction; occasional chromatolysis and

2. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Report of a Fatal Case with Autopsy, J. A. M. A. **112**:310 (Jan. 28) 1939.

neuronophagia; insignificant, if any, reaction of the neuroglia and microglia cells, and absence of vascular reaction, such as infiltrations of the adventitial spaces of the blood vessels with hematogenous cells or lipoids, which were occasionally present within physiologic limits in some ganglion cells but were absent in the glia and microglia. In all 5 cases the changes were alike, regardless of the varied nature of the chemical substances injected and of the fact that in cases 3 and 4 both insulin and metrazol had been used. The most pronounced changes were in the brain of the patient who had died in insulin shock. Not only were the aforementioned changes in evidence, but the rarefaction or edema of the tissues was pronounced. However, even in this case no inflammatory signs, such as perivascular infiltrations of the capillaries or blood vessels, were present.

The changes in the ganglion cells resembled those that have repeatedly been produced experimentally by injections of organic or inorganic poisons, such as phosphorus, arsenic or strychnine. In my cases the changes were occasionally associated with phenomena of satellitosis and neuronophagia, which may appear very early, within a few minutes after an injury to a ganglion cell. In legal electrocution,[3] for instance, the approximate interval between the application of the current and death is about two minutes. Yet, even in such cases it is possible to detect neuronophagia. This phenomenon is explained by the fact that ganglion cells in some layers of the cortex succumb before the glia cells. The latter evidently possess a greater vitality and therefore succumb more slowly, and thus have enough time to attack the dying or dead nerve cells. The same evidently obtains in the cases of fatal cell changes caused by poisonous substances, such as barbiturates and metrazol. However, the ganglion cells undergo not only morphologic changes, as pictured in figures 1, 2, 3, 4 and 5, but some abnormal physicochemical changes. Such changes in the cell elements of the parenchyma must reflect on the tissue fluids in which the cells are bathed. The tissue fluids carrying the waste of such cells to the subarachnoid space produce in the latter the morphologic changes classified as aseptic meningitis. The distended meshes of the parenchyma, denoting an excessive amount of interstitial tissue fluids, may account for the distended subarachnoid space, resembling in many instances external hydrocephalus. In this connection, a statement by Lemke [4] is of interest—that patients with marked internal and external hydrocephalus do not respond favorably to treatment and that such

3. Hassin, G. B.: Changes in the Brain in Legal Electrocution, Arch. Neurol. & Psychiat. **30**:1046 (Nov.) 1933; Changes in the Brain in Accidental Electrocution, J. Nerv. & Ment. Dis. **86**:668, 1937.

4. Lemke, R.: Ueber die Indikation zur Insulinshockbehandlung der Schizophrenie, Arch. f. Psychiat. **107**:223, 1938.

patients show an abnormal encephalogram. Structural changes in the meninges themselves, such as hyperplasia and thickening with formation of adhesions, were absent, suggesting that there was no direct action of the injected substances on the meninges themselves. On the whole, neither in the ganglion cells nor in the parenchyma or the subarachnoid space was there anything unusual in the changes, which, however, varied in extent and intensity. For instance, they often appeared more striking in the medulla oblongata, especially in the olives, but even there they presented no unusual features. Marked as were the changes in the ganglion cells, they were reversible, and only occasionally were they severe in individual cells. For this reason, they should not be considered as the cause of death or of such clinical manifestations as epileptic attacks, somnolence or coma. Rather, the edematous condition of the brain or stasis of its tissue fluids (with the consequent faulty removal of the toxins from the parenchyma to the subarachnoid space and the resulting toxemia) is to be considered more dangerous than the changes in the ganglion cells. Whether a so-called vasal factor is at play (Bodechtel,[5] Döring[6]), by causing a sudden collapse of the cerebral blood vessels, or the direct action of the poison on the cell body (Kobler,[7] Malamud and Grosh[8]) is the essential factor cannot be determined by histopathologic research; such a factor, however, is highly problematic. Nor is it possible to determine by histologic studies whether the cause of the edema is alkalosis (Wohlwill[9]), anoxia (MacKeith and Meyer[10]), hydremia or other abnormal physiologic or chemical phenomenon, resulting probably from disturbances of so-called circulation of the cerebral tissue fluids and the edema. Edema of the cerebral tissues has been mentioned by others (Bodechtel[5] and Scheiddeger[11]), but was emphasized

5. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, zugleich ein Beitrag zu seiner Pathogenese, Deutsches Arch. f. klin. Med. **175**:188, 1933.

6. Döring, G.: Zur Histopathologie und Pathogenese des tödlichen Insulinshocks, Deutsche Ztschr. f. Nervenh. **147**:217, 1938.

7. Kobler, F.: Histologischer Gehirnbefund nach Insulinkoma, Arch. f. Psychiat. **107**:688, 1938.

8. Malamud, N., and Grosh, L. D., Jr.: Hyperinsulinism and Cerebral Changes: Report of a Case Due to an Islet Cell Adenoma of the Pancreas, Arch. Int. Med. **61**:579 (April) 1938.

9. Wohlwill, F.: Ueber Hirnbefunde bei Insulinüberdosierung, Klin. Wchnschr. **7**:344, 1928.

10. MacKeith, S. A., and Meyer, A.: A Death During Insulin Treatment of Schizophrenia, with Pathological Report, J. Ment. Sc. **85**:96, 1939.

11. Scheiddeger, S.: Veränderungen des Zentralnervensystems bei Vergiftungen durch Schlafmittel (Babitursäuregiftungen), Schweiz. Arch. f. Neurol. u. Psychiat. **39**:388, 1937.

by Terplan,[12] Bowen and Beck [13] and Moersch and Kernohan [14] in a case of fatal insulin shock. It is suggested that the edema should be combated by injections of hypertonic solutions of such substances as dextrose or magnesium sulfate. These should be tried, at least in hopeless or dangerous conditions.

CONCLUSIONS

Barbiturates, insulin and metrazol produce morphologic changes in the ganglion cells of the brain, often associated with neuronophagia but without marked macroglial or microglial reactive phenomena.

The changes are diffuse and appear to be somewhat more marked in the medulla, especially the olivary bodies.

Distention of the subarachnoid space and the cerebral tissue spaces—edema—is a dangerous occurrence and is much more significant than the changes in the ganglion cells.

The changes in the ganglion cells are not specific, for they are the same regardless of the type of poison; they also resemble changes produced experimentally by injections of a variety of organic or inorganic poisons.

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12. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131 (July) 1932.

13. Bowen, B. D., and Beck, G.: Insulin Hypoglycemia: Two Cases with Convulsions; One Necropsy Report, Ann. Int. Med. **6**:1412, 1933.

14. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242 (Feb.) 1938.

HISTOPATHOLOGIC CHANGES IN THE BRAIN FOLLOWING EXPERIMENTAL INJECTIONS OF METRAZOL

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With the introduction of insulin and metrazol treatment of dementia praecox, the question arose whether organic changes in the central nervous system are produced by these new methods. In a previous paper [1] it was reported that convulsive doses of insulin injected into rabbits were followed by irreparable damage to the central nervous system if the total number of units of insulin injected per kilogram of body weight was larger than 60 (corresponding approximately to a total of 1,800 units for a patient weighing 60 Kg.).

Reports in the literature of histopathologic studies of the brain following injections of metrazol are not numerous. De Morsier, Georgi and Rutishauser [2] injected a convulsive dose of metrazol into 1 rabbit on nine different days. They did not observe any histopathologic changes in the brain. Another rabbit was killed by the injection of one massive dose of metrazol and showed only marked hyperemia of the brain. Strecker, Alpers, Flaherty and Hughes [3] studied the brains of 7 monkeys which had received injections of varying convulsive doses of metrazol and were killed at the end of the treatment. Of these 7 brains, 3 were normal. In 3 others scattered subarachnoid hemorrhages

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Read at a meeting of the Chicago Neurological Society, Dec. 16, 1937. A discussion on the paper was published in the transactions of the society (ARCH. NEUROL. & PSYCHIAT. **39**:1108 [May] 1938).

1. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

2. de Morsier, G.; Georgi, F., and Rutishauser, E.: Etude expérimentale des convulsions produites par le cardiazol chez le lapin, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:144, 1937.

3. Strecker, E. A.; Alpers, B. J.; Flaherty, J. A., and Hughes, J.: Experimental and Clinical Study of Effects of Metrazol Convulsions, Arch. Neurol. & Psychiat. **41**:996 (May) 1939. Alpers, B. J.: Personal communication to the authors.

were seen. Besides, there were isolated, mild changes in cortical neurons in the form of swelling or vacuolation. In 3 animals cells of the supraoptic nuclei showed loss of Nissl bodies and vacuolation of the cytoplasm. Stender,[4] using 3 rabbits and 2 cats, injected 40 mg. of metrazol per kilogram of body weight and studied the brains in sections stained with thionine. He observed subpial hemorrhages, but stated that both the neurons and the glia were normal.

Reports of the histopathologic changes in human brains after injections of metrazol are meager. Von Angyal and Gyárfás[5] described briefly the gross pathologic changes in a case in which the patient had received two injections of metrazol preceding death and had suffered from chronic endocarditis. Briner[6] saw autopsies in 2 cases following injections of metrazol; in 1 case the patient had had bilateral hypernephroma and goiter, and in the other, pulmonary embolism and pelvic thrombophlebitis. Recently, Hayman and Brody[7] reported another case of death following metrazol therapy, again without a detailed microscopic description. Four cases which we are studying will be published *in extenso* later.

METHOD AND MATERIAL

In the present study are reported observations and histopathologic studies on the brains of 23 rabbits given injections of metrazol. In imitation of the treatment of dementia praecox in man, a dose of metrazol that would produce a convulsive seizure was injected into an ear vein of the rabbits on two days of each week. The injection of from 12 to 16 mg. of metrazol (in a 10 per cent aqueous solution) per kilogram of weight was followed shortly by clonic convulsions, beginning in the cervical muscles and spreading to the muscles of the legs. Usually the minimal dose produced mild clonic contractions, and only with larger doses (20 mg. or more per kilogram) could pronounced tonic fits be elicited. The whole attack lasted from a few seconds to about one minute. The animals recovered quickly. The utmost care, however, was necessary to keep them alive for longer periods. Six rabbits died during or a few minutes after the convulsions, though only the average dose of metrazol had been injected. In the majority of cases it was possible to imitate the treatment of dementia praecox and to give from seven to twenty-seven injections, spread over a period of from two to six weeks. It seemed as if resistance to metrazol developed gradually; after from five to seven treatments the animal sometimes would not respond to a dose which had promptly produced a convulsion during the preceding experiment. A second dose had to be

4. Stender, A.: Ueber Provokation epileptischer Anfälle durch Cardiazol, München. med. Wchnschr. **84**:1893, 1937.

5. von Angyal, L., and Gyárfás, K.: Ueber die Cardiazol Krampfbehandlung der Schizophrenie, Arch. f. Psychiat. **106**:1, 1936.

6. Briner, O.: Ergebnisse der Konvulsionstherapie an der Psychiatrischen Klinik in Bern, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:118, 1937.

7. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Report of a Fatal Case with Autopsy, J. A. M. A. **112**:310 (Jan. 28) 1939.

injected, and during the following experiment the dose had to be increased. This experience is in contrast to the effect of insulin, which produced sensitization after the first week of treatment.

The animals which survived were killed by decapitation. At autopsy, the brains did not show any gross pathologic lesion, except scattered subarachnoid hemorrhages in 2 cases (rabbits 9 and 11, with fourteen and three injections, respectively). In animals which died during a convulsive seizure there was marked hyperemia of the brain. Of the 23 rabbit brains which were studied, 9 were selected for a more detailed report, which is summarized in the accompanying table. The histologic technic described in the previous paper [1] was used. The histologic report is confined to a comparative study of three structures, in order to avoid too voluminous a description.

Summary of Experimental Data and Pathologic Changes in Rabbits Subjected to Metrazol Shock *

Rabbit No.	Period of Treatment, Days	No. of Days of Injection	Days of Survival	Died or Killed†	Amount per Kg. Injected, Mg.	Total Amount of Metrazol Injected, Mg.	Encephalitis	Pathologic Changes in Cortex	Pathologic Changes in Striatum	Pathologic Lesions in Cornu Ammonis	Pathologic Rating
16	22	11	31	K	16	345	—	—	—	—	—
7	26	11	1	K	23	550	(+)	—	—	—	—
9	31	14	5	D	20	720	(+)	—	(+)	+	+
4	44	17	3	K	22	870	—	(+)	+	(+)	+
15	22	10	30	K	30	730	—	(+)	+	—	(+)
17	30	18	14	K	22	930	—	+	+	+	+
24	30	23	19	K	33	1,550	+	++	+	++	+++
22	26	21	0	D	31	1,800	—	+	+	++	++
23	38	27	11	K	28	1,820	(+)	(+)	+	++	++

* In this table, — indicates absence of pathologic changes; (+), mild changes (vacuolation of cytoplasm in acute conditions, or shrinkage of cytoplasm and nuclei with mild glial hypertrophy in progressive conditions); +, more marked changes (shrinkage of cytoplasm and nuclei, glial hypertrophy and hyperplasia, diminution in the number of neurons and neuronophagia), and ++, very marked changes (intensity of pathologic changes more severe than in +).

† K indicates that the rabbit was killed; D, that it died.

HISTOLOGIC REPORT

Rabbit 7.—There were isolated, small granulomas (encephalitis produced by Encephalitozoon) with a surrounding local increase in glia nuclei and mild perivascular round cell infiltration. No meningitis or generalized encephalitis was present.

Rabbit 9.—In the frontal cortex isolated encephalitozoon granulomas were seen; the diencephalon and midbrain were free. There was a diffuse hemorrhage into the pia-arachnoid covering the posterior third of the cerebral cortex, with indications of progressive organization. The neurons of the striatum showed a mild degree of vacuolation of the cytoplasm; the glia nuclei were increased in number. In the hippocampus, h_3 to h_5 of the cornu ammonis showed shrinkage and diminution in number of neurons, with concomitant proliferation of astrocytes.

Rabbit 4.—The brain was free from encephalitis. The cerebral cortex showed a definite increase in glia nuclei, with mild shrinkage of the cytoplasm of neurons. In the striatum the shrinkage of both cytoplasm and nuclei was more marked (fig. 2 *B*), and, in addition to a generalized increase in glia elements, there were instances of satellitosis. This glial hyperplasia with hypertrophy was also demonstrable in the hippocampus (fig. 4 *B*), where it accompanied a mild diminution in the number of neurons of the cornu ammonis.

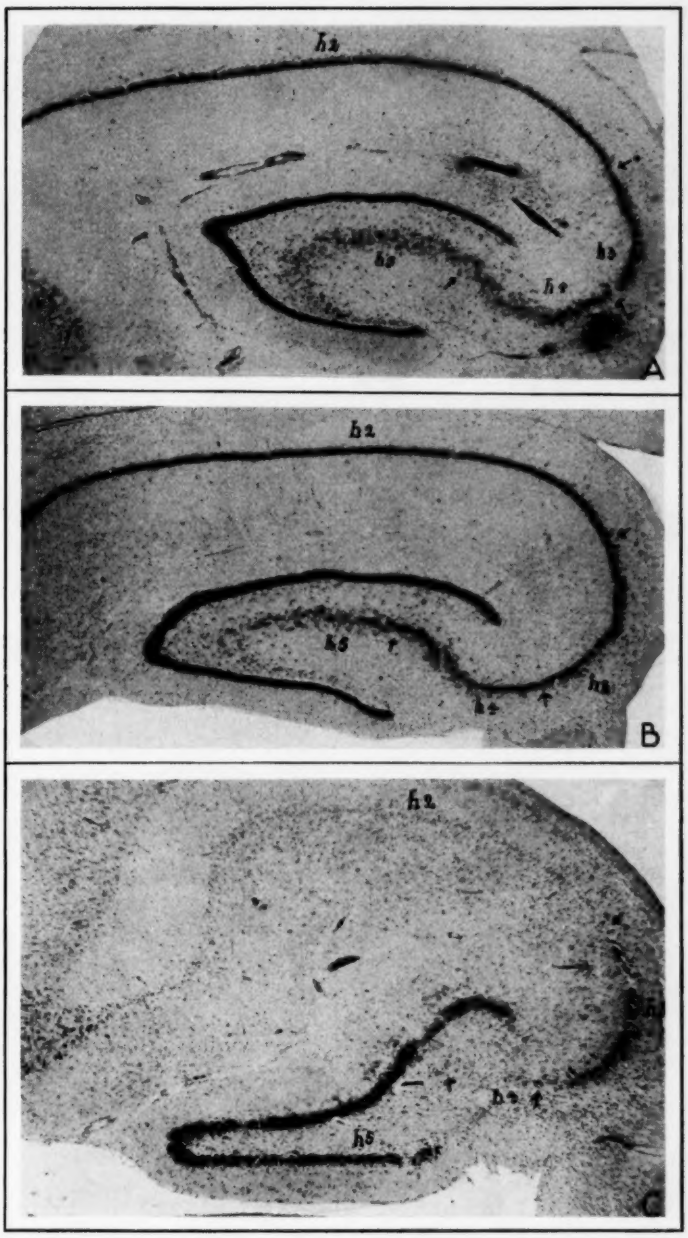

Fig. 1.—Sagittal sections through the hippocampus (cresyl violet stain; magnification, about 19 ×). *A* was taken from a control rabbit which was infected with Encephalitozoon cuniculi. The immediate environment of the granuloma only shows impairment of the cornu ammonis, and there is no generalized gliosis. *B* was taken from rabbit 4, into which a total of 870 mg. of metrazol had been injected. There are shrinkage and reduction in number of the neurons in the cornu ammonis. *C* was taken from rabbit 24, into which a total of 1,530 mg. of metrazol had been injected and which survived the last injection for nineteen days. Most of the neurons of the cornu ammonis have disappeared, with the exception of some shrunken cells in h_3. These is a considerable increase in glia nuclei.

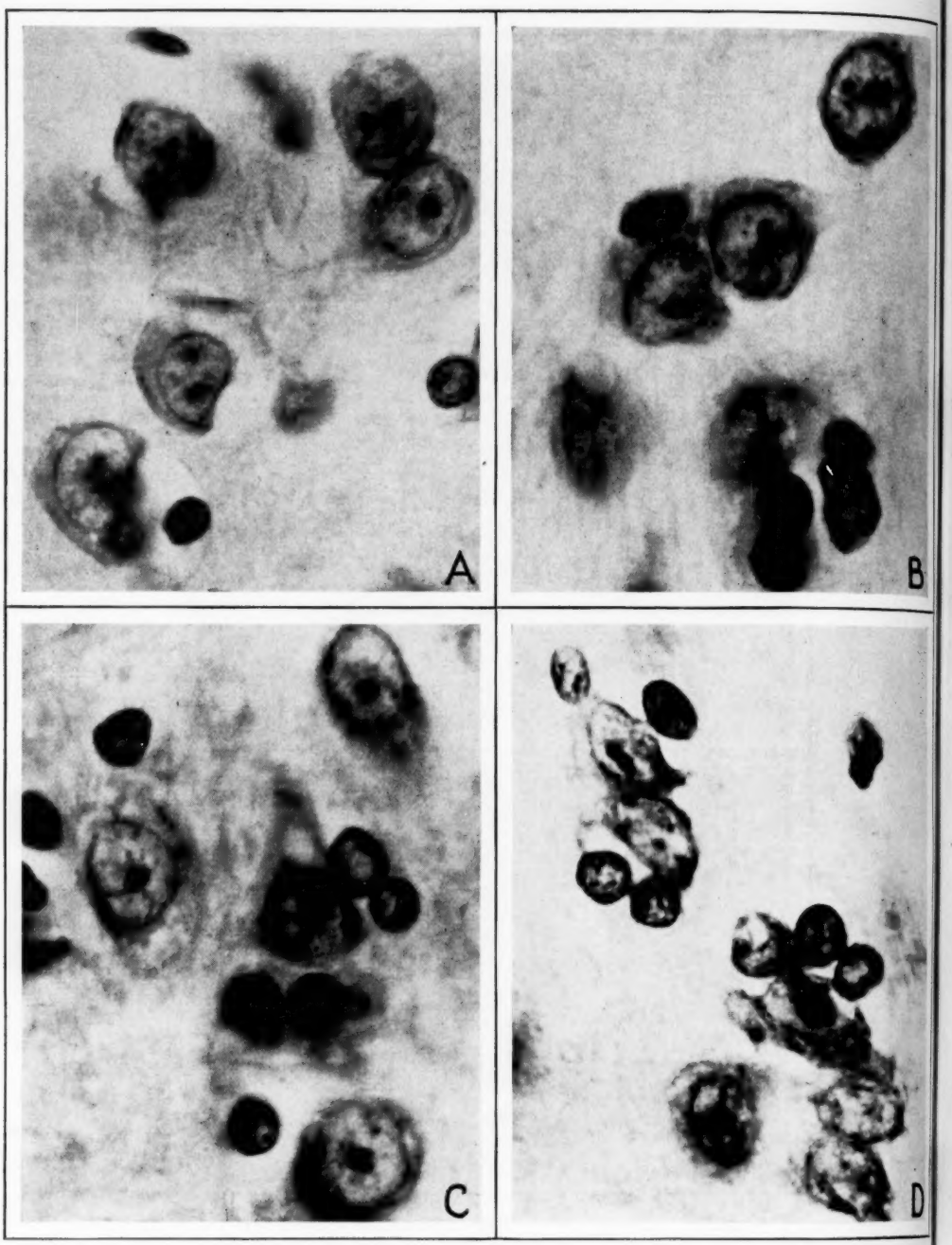

Fig. 2.—Sections of the striatum (cresyl violet stain; magnification, about 1265 ×). *A* is from a control rabbit; *B*, from rabbit 4 (same animal as that from which section shown in figure 1 *B* was taken), shows some shrinkage of cytoplasm and nuclei and a mild increase in oligodendroglia. *C* is from rabbit 22, into which 1,800 mg. of metrazol had been injected and which died during the last convulsion. There are swelling and vacuolation of the cytoplasm of the neurons and increase in satellite cells. *D*, from rabbit 24 (same animal as that from which section shown in figure 1 *C* was taken), shows considerable atrophy of neurons with beginning neuronophagia.

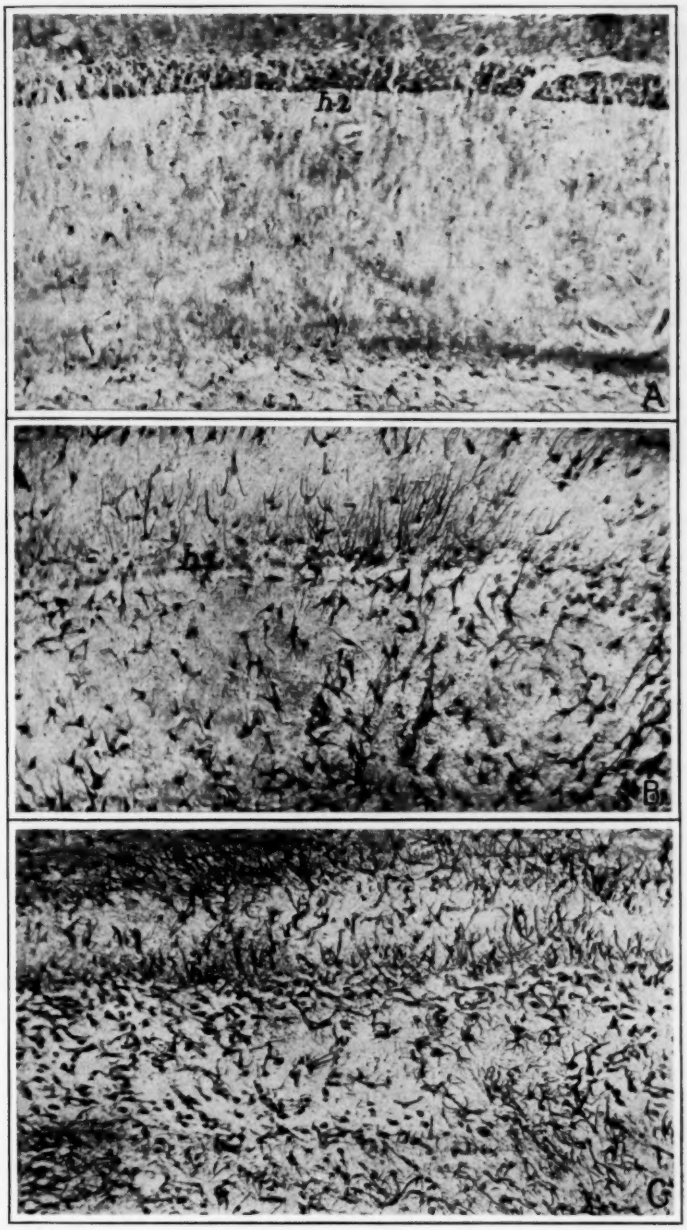

Fig. 3.—Sections of the hippocampus, with h_2 of the cornu ammonis (Cajal's gold-sublimate stain; magnification, about 104 ×). *A* is from a control rabbit (same animal as that from which section in figure 1 *A* was taken). *B* is from rabbit 22 (from which section in figure 2 *C* was taken) and shows hypertrophy and hyperplasia of astrocytes. *C* is from rabbit 24 (from which section in figure 1 *C* was taken) and shows marked hypertrophy and hyperplasia of astrocytes.

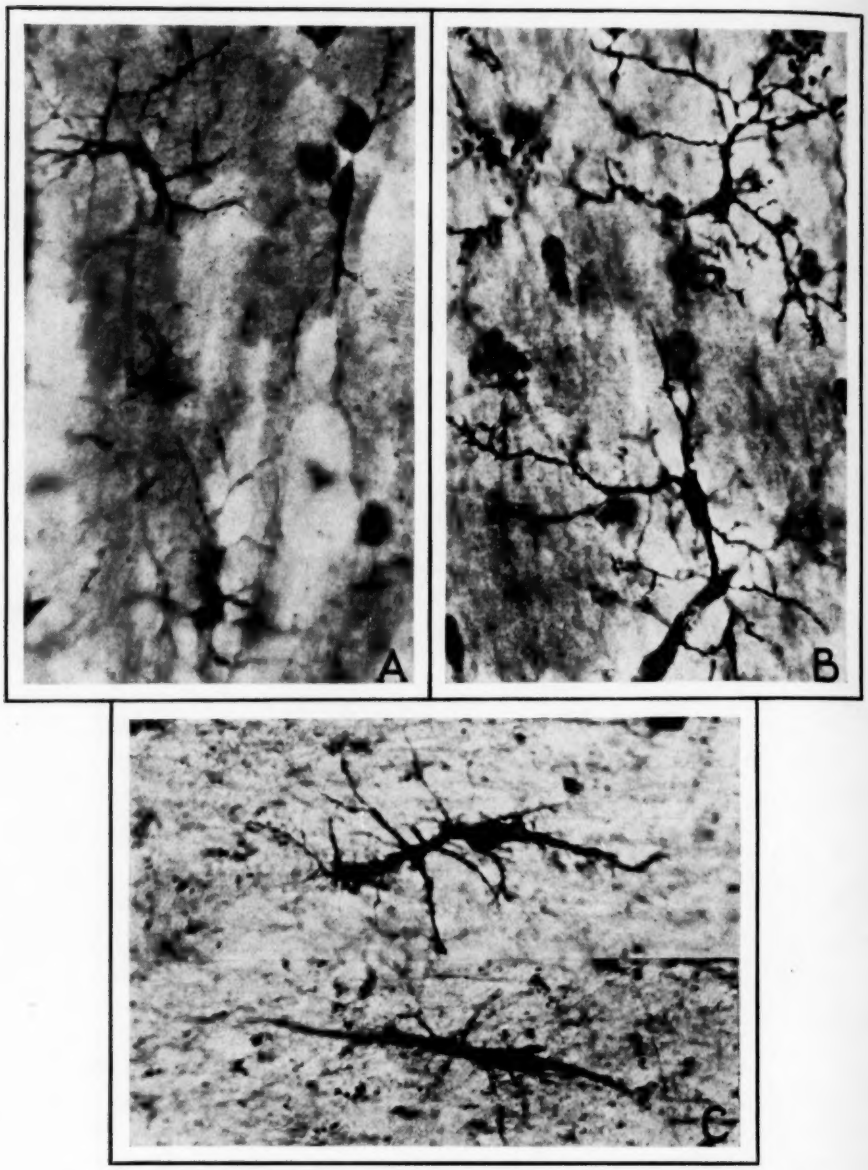

Fig. 4.—Sections of the hippocampus at h_2 (Kanzler's modification of del Rio-Hortega's method for microglia; magnification 790 ×). *A* is from a control rabbit (same animal as that from which section in figure 1 *A* was taken). *B* is from rabbit 4 (same animal as that from which section in figure 1 *B* was taken) and shows hypertrophy of microglia. *C* is from rabbit 23, into which a total of 1,820 mg. of metrazol had been injected and which was killed on the eleventh day after the last injection. The section shows hypertrophy of microglia, with the formation of rod cells.

RABBIT 15.—No encephalitis could be detected microscopically. The cortical neurons appeared intact; there was a mild increase in glia nuclei. In the striatum there was a mild degree of shrinkage of cytoplasm and nuclei alike, with an increase in the number of satellite glia cells. Gliosis, not marked, was present in the cornu ammonis.

RABBIT 17.—No inflammatory reaction was present. The deeper layers of the cerebral cortex (V to VI) contained many shrunken neurons and nuclei, with folded membranes. No significance was attributed to the many dark-staining, shrunken neurons in the upper layers, which may also be observed in normal rabbit brains after fixation in formaldehyde. There was a definite increase in the number of satellites and interstitial glia cells. The same picture was seen in the striatum, together with scattered instances of neuronophagia. In the cornu ammonis the neurons of h_4 and h_5 seemed to be diminished in number, and the remaining neurons were shrunken and stained deeply. There was a mild degree of glial hyperplasia.

RABBIT 24.—In this brain encephalitozoon encephalitis was somewhat more pronounced than in the brains of rabbits 7 and 9, though it did not attain the intensity demonstrated in the photograph from a control animal (fig. 1). The cornu ammonis was spared, and there was no meningitis. In the cerebral cortex the shrinkage of both nuclei and cytoplasm was much more pronounced than in the preceding cases, and there was marked glial hyperplasia. The same was true of the striatum, which showed numerous instances of neuronophagia, in addition to a marked increase in satellite glia cells (fig. 2 *D*). The cornu ammonis had almost completely disappeared; only a few neurons had survived in h_3 (fig. 1 *C*). The structure had been covered by a dense meshwork of proliferated astrocytes and microglia cells (fig. 3 *C*).

RABBIT 22.—No inflammatory reactions were visible in the cortex, striatum and cornu ammonis. As a whole, the pathologic condition of the neurons and the glia resembled closely the changes described in rabbit 24, though they were less pronounced. The cornu ammonis as a whole was preserved, but there was a definite reduction in the number of neurons throughout (figs. 2 *C* and 3 *B*).

RABBIT 23.—One or two granulomas were to be seen in sagittal sections through the whole brain; the cornu ammonis was free of encephalitis. Again, the histopathologic changes were shrinkage of cytoplasm and nuclei with glial hyperplasia and hypertrophy, which was mild in the cortex and more pronounced in the striatum and cornu ammonis. Hypertrophy of the microglia led to the formation of many large, solid rod cells (fig. 4 *C*).

COMMENT

In evaluating the histopathologic changes, it seems that the time factor plays an important role in the change in the microscopic picture. First may be considered the brains of the rabbits which did not receive more than 750 mg. of metrazol and which died during an attack or were killed the day after. It seems that the outstanding feature was mild vacuolation of the cytoplasm of the different neurons, together with mild hypertrophy and hyperplasia of all three types of glia elements. With increasing doses, length of treatment and time of survival, the picture changed to shrinkage of both cytoplasm and nuclei, with folding of their membranes, and there was diminution in the number

of neurons, with increasing degrees of neuronophagia. The hypertrophy and hyperplasia of both astrocytes and microglia cells, too, paralleled the dose injected and the time of survival. The best examples were rabbits 22, 23 and 24, which had been given injections of total amounts of from 1,550 to 1,820 mg., and rabbits 4 and 17, which received 870 and 930 mg., respectively. The diminution in the number of neurons of the cornu ammonis was more pronounced in rabbits 24 and 17, which survived for nineteen and fourteen days, respectively, than in rabbits 22 and 4, which were killed on the day following the last injection. Such experiences would correspond to observations made in human brains in cases of epilepsy or of vascular disease. Though the ganglion cell may be functionally severely impaired, its skeleton disappears only gradually. On the other hand, the stimuli given to glial overgrowth only gradually assert themselves, and the maximum of hypertrophy and hyperplasia may be observed only after the passing of weeks.

A disturbing influence in evaluating histopathologic changes in the rabbit brain is the frequent presence of Encephalitozoon cuniculi encephalitis in the form of granulomas, perivascular inflammatory reactions and meningitis. However, experience will teach one to differentiate such local changes with limited glial reaction from the more generalized experimental lesion. Furthermore, in this investigation only the brains of rabbits were selected for histopathologic studies which either were free of encephalitis or showed only isolated formation of granulomas in parts of the brain other than the nuclei which were chosen for detailed study. On the other hand, as controls rabbit brains were selected which showed marked encephalitic changes (fig. 1 *A*).

The physiopathologic basis for the histopathologic changes seems to be anemia brought about by two different mechanisms. On the one hand, after injections of metrazol there seems to be an initial, sudden contraction of cerebral arteries, which is followed by hyperemia. Selbach [8] stated that in rabbits, after injections of metrazol, the blood vessels of the ear and the retina disappeared, but that there was soon "persistent and continuous venous hyperemia." Steinberg, Heilbrunn and Liebert [9] observed severe pallor of the surface of the rat brain at the beginning of a convulsive seizure. However, in rabbits which died during a convulsion there was marked hyperemia of the brain.

It is of interest to point out the difference in the physiopathologic effect and the histopathologic changes produced by insulin and those

8. Selbach, H.: Ueber intravenöse p_H Messungen im experimentellen epileptischen Anfall (durch Cardiazol), Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:334, 1937.

9. Steinberg, L.; Heilbrunn, G., and Liebert, E.: Evaluation of the Newer Treatment of Dementia Praecox, Illinois M. J. **75**:405 (May) 1939.

by metrazol. The effect of insulin seems to be essentially a deprivation of the neurons of dextrose, which, in turn, prevents utilization of oxygen. The effect of metrazol is a combination of a sudden transitory vasospasm and interference with tissue respiration, probably by disturbance in equilibrium of the complicated system of respiratory ferments.[10] It would not do justice, however, to the complicated physiologic processes involved in these experimental convulsions if one tried to explain all histopathologic changes on the basis of anemia alone. At the same time there are changes in the hormonal equilibrium of the body, changes in the base-acid equilibrium, a shift in the potassium-calcium balance with a rise in calcium (Georgi[11]) and a change in the water distribution, resulting in a "dry" brain. Such changes, of course, influence in a "toxic" way the metabolism of the brain and, if lasting over longer periods, will damage the sensitive neurons. The difference in the effect of insulin and that of metrazol is also one of time. While the insulin shock takes place over a period of two hours, the effect of metrazol is crowded into a few minutes.

Comparison of the histopathologic changes in rabbits produced with injections of insulin and those produced with metrazol reveals that in the first group the cerebral cortex was earlier and more severely affected while in the second group the striatum and hippocampus showed the more marked changes. When equal periods of treatment are compared, it seems that the diminution in the number of neurons, the hyperplasia and hypertrophy of macroglia and microglia and the neuronophagia were much more pronounced in the second group.

SUMMARY AND CONCLUSIONS

Metrazol, in a 10 per cent solution was injected intravenously twice a week into rabbits, in imitation of the treatment of dementia praecox in man. The average dose injected was 22 mg. per kilogram of body weight and was sufficient to produce a convulsive seizure. Resistance to metrazol developed gradually, and the initial dose had to be increased after about five to seven injections.

Definite histopathologic changes were observed after injections of a total of more than 700 mg. of metrazol. The intensity of these changes was roughly parallel to the dose injected, the number of injections and the time of survival after the last injection. They were characterized by more or less severe shrinkage of both cytoplasm and nuclei of neurons and hyperplasia and hypertrophy of the different types of glia cells. The pathologic effect was more pronounced in the striatum and hippocampus than in the cerebral cortex.

10. Labes, R.; Wedell, K., and Soehring, K.: Beziehungen zwischen der Wirkung von Krampfgiften und Störungen der Gewebsatmung, Arch. f. exper. Path. u. Pharmakol. **185**:379, 1937.

11. Georgi, F., and Strauss, R.: Problem of Convulsions and Insulin Therapy, Am. J. Psychiat. (supp.) **94**:76, 1938.

MODE OF ACTION OF BRILLIANT VITAL RED IN EPILEPSY

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In a previous paper [1] evidence was presented which tends to support the hypothesis that epilepsy is closely related to a disturbance in the metabolism of the vital lipids cholesterol and lecithin. The biochemical effects of these lipids and the known facts concerning epilepsy which contribute to this conception were reviewed. Parenteral injections of cholesterol were found to have a protective effect on white mice with experimental epilepsy induced by cocaine hydrochloride. Furthermore, it was observed that the convulsive effects were later in onset in the mice protected by cholesterol than they were in the groups used as controls. This was interpreted as indicating a delayed absorption of the convulsive agent. The protective effect, likewise, was explained on this basis. The results of the study were thus interpreted as consistent with the theory that the vital lipids play a significant role in the permeability of cell membranes and, through this mechanism, are an important factor in epilepsy. The purpose of this report is to present evidence which was found to support, even more conclusively, the same point of view.

In the course of their investigations, Cobb, Cohen and Ney [2] discovered that brilliant vital red (Evans), a supravital dye,[3] tends to raise the convulsive threshold in rabbits for triphenylphosphite, camphor liniment U. S. P., picrotoxin and strychnine sulfate, used in induction of experimental epilepsy. The same dye was found, further, to be of value in the treatment of human epilepsy. That a protective agent of nonsedative character has been found, effective in the management of both human and experimental epilepsy, is important. An experimental approach to the problem of human epilepsy is thus opened, which

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This study was aided by a grant from the Child Neurology Research (Friedsam Foundation).

1. Aird, R. B., and Gurchot, C.: Protective Effect of Cholesterol in Experimental Epilepsy, Arch. Neurol. & Psychiat. **42**:491 (Sept.) 1939.

2. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, J. Nerv. & Ment. Dis. **85**:438-441, 1937; Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156-1177 (Dec.) 1938.

3. The chemical formula for brilliant vital red is tolidine + 1 mol of β-naphthylamine-3,6-disulfonic acid + 1 mol of β-naphthylamine-6-monosulfonic acid.[2]

may prove to be of considerable significance. If the protective mechanism of brilliant vital red in experimental epilepsy could be explained a new understanding of important factors underlying human epilepsy might be realized.

Accordingly, the following studies on brilliant vital red have been made: (1) verification of the protective effect of brilliant vital red in both experimental and human epilepsy; (2) studies concerned with the mode of action of brilliant vital red in epilepsy.

I. BRILLIANT VITAL RED AS A PROTECTIVE AGENT IN CONTROL OF EPILEPSY

A. Experimental Epilepsy.—The susceptibility of white mice to certain convulsive agents was determined on a statistical basis, by a method similar to that used in the study on cholesterol.[1] The criteria of involvement were the same, and susceptibility was recorded as the most severe stage attained by each mouse. The convulsive agents were chosen for their predominating effect at different levels of the central nervous system. Cocaine hydrochloride was selected for its predominant cortical effect, picrotoxin for its effect on the midbrain and strychnine sulfate for its effect on the spinal cord. After preliminary tests with these convulsive agents, the following doses, per kilogram of body weight, were adopted for this study: 96 mg. of cocaine hydrochloride; 2.4 mg. of picrotoxin, and 1 mg. of strychnine sulfate. In a second series, white mice were stained with brilliant vital red. Six subcutaneous injections of 0.1 cc. of a 1 per cent solution of the dye were given over a period of eight days and resulted in a sufficiently intense degree of staining for the purposes of the study. These mice were similarly tested with the three convulsive agents, the dosage and conditions, other than the staining, being identical with those for the control group. The results of these studies, shown in table 1, amply confirm the findings of Cobb and his associates.[2]

B. Human Epilepsy.—Six epileptic patients were selected for study because of their failure to respond, after prolonged trial, to any accepted method of treatment. Such a selection, of course, would be improper from the standpoint of obtaining a fair evaluation of the clinical value of brilliant vital red in treatment of epilepsy, but was thought to be adequate to verify the observation of Cobb and his co-workers [2] on the protective effect of brilliant vital red in human epilepsy. The essential points in these cases, with a description of the convulsive states before and after treatment with brilliant vital red, are presented in the following brief reports.

REPORT OF CASES

CASE 1.—K. M., a youth aged 17, had seizures of numbness, which started at 8 years of age. In the past one and a half years he had experienced almost daily petit mal attacks, of from seven to eight seconds' duration. Moderately severe grand mal seizures, lasting from one to two minutes, occurred every one or two months during the same period. An aura of anxiety and disorientation was associated with the major attacks. No focal signs or symptoms had been observed. The patient had sustained a fall at 3 years of age but made a good recovery, without sequelae. He had a tonsillectomy at 8, and a sinus was drained at the age of 15. He was chronically constipated.

Physical and neurologic examinations gave essentially normal results. Examination of the cerebrospinal fluid showed 12 lymphocytes, 6 red cells and a positive reaction for globulin. The laboratory findings were otherwise normal. Encephalograms were interpreted as normal. A diagnosis of convulsive state, of undetermined origin, was made.

Three and one-tenth grams of a 1 per cent solution of brilliant vital red was injected intravenously in amounts of from 30 to 40 cc., eight injections being given during a period of ten days. This treatment resulted in a moderately intense degree of staining of the skin, conjunctivas and mucous membranes.

The patient's seizures were definitely less severe and frequent during a follow-up period of six months. The attacks were almost all of the petit mal type, with a duration of from two to three seconds, and occurred at intervals of three or four days. In the six months there were only 4 attacks with complete loss of consciousness. These were tonic fits, which lasted about one minute and were not complicated by a clonic phase.

TABLE 1.—*Protective Effect of Brilliant Vital Red on Production of Experimental Epilepsy in White Mice*

Mice	Convulsive Agent	Dose, Mg. per Kg. of Body Weight	No. of Mice	Effects				Convulsive Involvement, %
				No Convulsion	Petit Mal	Grand Mal	Fits and Death	
Controls	Strychnine sulfate	1	29	11	1	2	15	62
	Picrotoxin	2.4	40	6	9	25	0	85
	Cocaine hydrochloride	96	87	31	10	22	24	64
After staining with brilliant vital red	Strychnine sulfate	1	27	27	0	0	0	0
	Picrotoxin	2.4	39	18	5	16	5	67
	Cocaine hydrochloride	96	29	23	2	3	1	20

CASE 2.—V. G., a woman aged 22, had had grand mal epilepsy for three years. Seizures were rare at first, but occurred frequently in the past one and a half years. The spells lasted from three to four minutes and usually came just before the menstrual period. Limitation of fluids, a ketogenic diet and sedation had been tried, without effect. The patient had suffered a "nervous breakdown" four and a half years before. A twin sister had seizures similar to those of the patient.

Physical and neurologic examinations gave essentially normal results. Routine laboratory tests revealed nothing abnormal. Encephalograms were interpreted as normal. A diagnosis of convulsive state, of undetermined origin, was made.

Two and seven-tenths grams of a 1 per cent solution of brilliant vital red was injected intravenously in seven daily injections of from 30 to 40 cc. The skin, conjunctivas and mucous membranes were well stained.

Attacks continued to occur at about the same intervals, but were definitely less severe. All attacks were of the petit mal type and consisted of a feeling of faintness without total loss of consciousness. These spells lasted only five or six seconds. There were no grand mal attacks in a period of six months.

CASE 3.—E. I., a girl aged 9, had had encephalitis when she was 1 year old. Generalized tonic seizures, lasting about thirty seconds, without loss of conscious-

ness, started at the age of 1½ years. In the past three or four years the attacks had become more frequent, occurring three or four times a day, and were also more severe. The attacks were characterized by an aura, lasting one or two seconds, and a tonic and clonic phase, lasting about two minutes, and were followed by sleep. A ketogenic diet, phenobarbital and restriction of fluids had been tried, without effect.

Physical and neurologic examinations revealed only slight mental retardation. Laboratory tests, including encephalograms, showed nothing abnormal. A diagnosis of convulsive state, of postencephalitic origin, was made.

Two and a half grams of a 1 per cent solution of brilliant vital red was injected intravenously in nine injections, during a period of ten days, and resulted in moderately intense staining.

The patient had about 8 spells per month in the seven months following the injections of brilliant vital red. The attacks were all very light and of the petit mal type. They were preceded by a brief aura and lasted only one or two seconds. The patient did not completely lose consciousness or fall with these attacks.

CASE 4.—E. G., a man aged 30, had had acute osteomyelitis of the right humerus at 16 years of age, which had metastasized to the left parietal portion of the skull, with formation of an abscess. Jacksonian fits on the right side and anomia developed in association with the abscess. The anomia was complete for one month and then slowly subsided, except for a slight residuum. Seizures persisted on the right side, but the attacks were chiefly of the petit mal or light grand mal type after the drainage of an extradural abscess, at the age of 27. The patient had suffered approximately 40 attacks per month during the past three years.

Physical and neurologic examination showed a depression in the left temporoparietal region of the skull. Frequent twitching and spasm of the muscles of the right side of the face and neck were observed. There were residual anomia and a slight hesitancy in speech. The right knee jerk was increased, as compared with the left. Routine laboratory tests gave normal results. An encephalogram showed that the right lateral ventricle was slightly dilated and larger than the left. The supracortical subarachnoid spaces were absent on the left side. A diagnosis of convulsive state, of jacksonian type, associated with cortical adhesions and a possible scar of the left parietal portion of the brain, was made.

Because of the relation of the cortical process to the motor and speech centers, operative intervention was considered inadvisable. Three and one-tenth grams of a 1 per cent solution of brilliant vital red was injected intravenously in amounts of from 30 to 40 cc. Eight injections were given in a period of nine days and resulted in a brilliant stain.

The patient's attacks were reduced to 20 in the first month, 24 in the second month, 29 in the third month and 36 in the fourth month following staining. All the attacks were of the petit mal type and were definitely briefer and less severe than the seizures before staining. However, in the third and fourth months there were a gradual increase in the severity of the attacks and an approach to the condition before injection.

CASE 5.—H. G., a man aged 35, was struck on the occiput in 1917 and was unconscious for several hours. He remained in a semicomatose condition for two weeks. Fracture of the skull was not demonstrated roentgenographically. Petit and grand mal seizures occurred from the time of the accident. The attacks were not preceded by an aura and were not focal in character. Repeated physical examinations and two encephalograms, made on four admissions to the hospital

between 1920 and 1932, revealed nothing abnormal. Phenobarbital relieved the condition at first, but in spite of its use and a ketogenic diet the attacks became more numerous. Typhoid vaccine and diathermy were tried without definite effect. At the time of his fifth entry to the hospital the patient was having about 40 or 50 attacks per month. Approximately one third of the attacks were of the grand mal type.

Physical and neurologic examinations showed an essentially normal condition, except for slight slowing of the mental processes. The laboratory findings were normal. A diagnosis of post-traumatic convulsive state was made.

Six grams of a 1 per cent solution of brilliant vital red was injected intravenously in amounts of from 20 to 40 cc. in twenty injections during a period of three and a half weeks. The patient was brilliantly and deeply stained. Daily urinalyses throughout the period of injection, as well as occasionally during the follow-up period, gave normal results.

The attacks were less severe and frequent after the sixth injection, and the patient had only 2 spells in the last twelve days of hospitalization. From 20 to 30 attacks per month occurred in the following nine months. These were chiefly of the petit mal type, but light grand mal seizures, lasting one or two minutes, occurred on an average of twice a month.

CASE 6.—J. F., a girl aged 17, had had convulsions for three and a half years. The seizures at first were rare, but became progressively more frequent, until there were several daily. The attacks usually occurred early in the morning and tended to be more frequent and severe at the time of the menstrual periods. The attacks were characterized by a sudden onset, without aura. The patient fell, and loss of consciousness was quickly followed by a generalized tonic state, which then developed into a typical clonic fit of from four to five minutes' duration. In addition to the grand mal attacks, there were spells of petit mal, which usually occurred several times a day and were not associated with focal signs or symptoms. Ketogenic diet, limitation of fluids, phenobarbital, glandular therapy and numerous "mail order" forms of treatment had been tried, without benefit. Removal of an impacted tooth and adjustment of glasses had not helped.

Physical examination showed acne vulgaris and a moderate degree of myopia. Neurologic examination revealed a delayed reaction time, hyperactive deep and superficial reflexes and a Hoffmann sign bilaterally. Routine laboratory examination revealed nothing abnormal. A five hour dextrose tolerance test gave normal results. Encephalograms were normal. The cerebrospinal fluid gave positive reactions for protein and globulin, and the colloidal gold curve was 0112100000. A diagnosis of convulsive state, of undetermined origin, was made.

Two and forty-five hundredths grams of a 1 per cent solution of brilliant vital red was injected intravenously in seven injections during a period of one week and resulted in a moderate degree of staining of the skin, mucous membranes and conjunctivas.

Both petit and grand mal seizures continued to occur in the five month period during which this patient was observed, but the attacks were definitely less severe and frequent than prior to treatment. The petit mal spells occurred only once or twice daily and lasted only two or three seconds. The grand mal seizures diminished to from 6 to 9 per month. These attacks lasted two or three minutes and were considerably less severe than before treatment.

Summary.—Of 6 patients suffering from severe and varied forms of epilepsy, chosen because they had failed to respond to any accepted

type of treatment, 5 showed from slight to marked improvement in frequency of the attacks, and the attacks of all 6 were reduced in duration and severity. The improvement lasted for from four to seven months. Thus, as in the experimental work, the findings of Cobb and his co-workers were confirmed.

II. MODE OF ACTION OF BRILLIANT VITAL RED IN EPILEPSY

Three possible modes of action may be considered in explanation of the protective mechanism of brilliant vital red in epilepsy. First, the dye might exert a protective effect directly on the central nervous system. Such an effect would necessarily involve the entrance of the dye into the central nervous system and presumably would act at the cortical level to alter its threshold of stimulation. Since in the case of experimental epilepsy the convulsive agent must reach the brain in certain concentrations before a convulsion can be produced, two other possible modes of action may be considered. It is conceivable that some action might occur locally in the tissues between the convulsive agent and the dye to prevent the former from reaching the central nervous system, at least in adequate concentrations and in an active form. Such an effect presumably would involve some form of chemical interaction —neutralization or chemical bonding. Third, the dye might produce alterations in tissue permeability, the effect of which would be to set up a barrier to the convulsive agents between the central nervous system and the rest of the body. The logical tissue barriers for this sort of effect would be the endothelium of the hematoencephalic barrier and the cell membranes of the cortical cells which are concerned physiologically with the convulsive state.

A fourth hypothesis is that the dye conceivably may have an inhibitory influence on the effector mechanism of the neuromuscular system—presumably an effect like that of curare acting at some synaptic level, which would abolish the peripheral tonic and clonic manifestations of epilepsy. Since, however, the central manifestations of the convulsive state (such as the aura and loss of consciousness) would still remain and this type of reaction is not characteristic of the protection afforded by brilliant vital red, this hypothesis may be dismissed.

A. STUDIES CONCERNED WITH THE POSSIBILITY THAT BRILLIANT VITAL RED ACHIEVES ITS PROTECTIVE ACTION AS A RESULT OF A CENTRAL EFFECT ON THE BRAIN TISSUE PROPER

1. EXPERIMENTAL STUDIES.—In the studies on mice (table 1) it was found that brilliant vital red protected against convulsive agents, which presumably act at different levels of the central nervous system, and, in fact, protected better against

strychnine than against other drugs which act at higher levels. This suggests that the protective effect of the dye is not limited to the cortex and that if the protection is a "blanket" effect involving the whole central nervous system, it operates relatively inefficiently at the cortical level.

2. Histologic Studies.—Examination of the brains of both mice and dogs at all stages of staining with brilliant vital red failed to reveal the dye. The meninges were stained light pink, but the cortex and subcortical tissue were as clear and normal in appearance as the corresponding tissues in unstained animals. Detailed histologic studies verified these gross observations. With the technic described by Evans and Scott,[4] specimens of tissue from various portions of the cortex and subcortical areas of stained mice and dogs were placed on glass slides, bathed in Ringer's solution, flattened gently with a cover slip and examined at all magnifications. The absence of significant changes was in entire agreement with the results reported by Evans and Schulemann.[5] In their exhaustive studies on staining with brilliant vital red, McCurdy and Evans[6] and Evans[7] observed that the dye entered the central nervous system only in the presence of a profound disturbance; for example, the anterior horn cells stained when they had been injured by poliomyelitis.

3. Spectrographic Studies.—If brilliant vital red enters the central nervous system and produces its protective action at this site, presumably it passes through the cerebrospinal fluid before reaching the brain. Also, as suggested by the observations of Evans and Scott[4] on staining and "decolorization," a "balance" must exist between the intracellular deposits and the extracellular concentration of the dye in tissue stained with brilliant vital red. "Extracellular concentration" in the case of the brain would be the concentration of the dye in the cerebrospinal fluid. Therefore, successful staining of the tissues of the central nervous system would necessarily involve staining of the cerebrospinal fluid. Since such staining might well be so slight as to be undetectable by gross examination, spectrographic studies[8] were made of the cerebrospinal fluids of dogs intensely stained with brilliant vital red. Control studies showed that a 0.0001 per cent solution of the dye was readily detected by the spectroscope. The test is thus sensitive to more than 1 part in 500,000. Since repeated examinations of the cerebrospinal fluid of dogs at all stages of staining failed to reveal the dye, it was concluded that the dye, if present at all in the central nervous system, was in such minute concentrations as to be physiologically negligible, at least for the striking protective effects observed in these studies.

4. Threshold Determinations.—Conclusive evidence as to whether the protective effect of brilliant vital red occurred in the brain might be obtained by experimental determinations of the convulsive thresholds of animals before and after

4. Evans, H. M., and Scott, K. J.: On the Differential Reaction to Vital Dyes Exhibited by the Two Great Groups of Connective-Tissue Cells, Publication 273, Carnegie Institution of Washington, 1919, pp. 1-55.

5. Evans, H. M., and Schulemann, W.: The Action of Vital Stains Belonging to the Benzidine Group, Science **39**:443-454, 1914.

6. MacCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. **49**:1695, 1912.

7. Evans, H. M.: The Physiology of Endothelium, Anat. Rec. **8**:99-101, 1914.

8. The spectrographic studies were made in collaboration with Louis Strait, Ph.D., of the department of physics, University of California.

staining with the dye. If the dye physiologically has the effect of a central-acting anticonvulsant, the convulsive threshold of the cerebral cortex should be raised. In determinations of the convulsive thresholds of cats by electrical stimulation, Merritt and Putnam [9] showed that there is no change under the influence of brilliant vital red.

Summary.—The experimental impression that the protection afforded by brilliant vital red against epilepsy is not achieved by direct action on the central nervous system was substantiated by histologic and spectrographic studies on the brain and the cerebrospinal fluid, respectively, of animals. These studies failed to demonstrate the presence of the dye within the central nervous system following intense staining. This result was confirmed by Merritt and Putnam,[9] who showed by experimental determinations of the convulsive threshold of cats before and after staining with brilliant vital red that the dye had no central anticonvulsant effect.

B. STUDIES CONCERNED WITH THE POSSIBILITY OF A CHEMICAL BONDING OR NEUTRALIZING ACTION BETWEEN BRILLIANT VITAL RED AND THE CONVULSIVE AGENTS

1. STUDIES ON EXPERIMENTAL EPILEPSY (table 1).—It was found that brilliant vital red protects against such chemically varied drugs as cocaine hydrochloride, picrotoxin and strychnine sulfate. Cobb and his co-workers also found that the dye protects against triphenylphosphite and camphor liniment. This "blanket" type of protection against convulsive agents of entirely different chemical structures argues against any chemical bonding as the explanation of the protective mechanism of brilliant vital red.

2. STUDIES USING THE TECHNICS OF DIALYSIS AND ELECTROPHORESIS.[10]—A mixture of a 1 per cent solution of brilliant vital red and 0.05 per cent cocaine hydrochloride was placed in a collodion bag, which was then immersed in a bath of distilled water. After twenty-four hours drops of the distilled water were evaporated on a microscopic slide, and estimations of crystals were made under the microscope. A similar procedure was carried out with a mixture of 1 per cent brilliant vital red and 0.05 per cent strychnine sulfate placed in the collodion bag. In both instances the molecular concentration of the brilliant vital red was considerably in excess of that of the convulsive agent. If any chemical action occurred between the dye and the drug, the latter presumably would have been taken up completely, which thus would have prevented its escape from the bag to any great extent. Since in both instances the respective crystals were found in large numbers in the dialysate, it was concluded that no chemical reaction or bonding effect between the dye and the drugs had occurred.

A mixture of a 1 per cent solution of brilliant vital red and 0.05 per cent cocaine hydrochloride was placed in an electrophoresis apparatus. Under the influence of the current the brilliant vital red gradually migrated toward the

9. Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938.

10. These studies were made in collaboration with Charles Gurchot, Ph.D., of the department of pharmacology, University of California Medical School.

anode. When the process had been completed to the extent that the middle and cathode portions were colorless, specimens from these portions were examined under the microscope for cocaine crystals, as in the studies on dialysis. A solution containing 1 per cent brilliant vital red and 0.05 per cent strychnine sulfate was similarly studied. In both instances the crystals were present in about the same number in the middle and the cathode portion. Since the convulsive drugs did not participate in the movement of the dye, it seems safe to conclude that the dye and drugs remained independent of one another, that is, that no chemical interaction or bonding effect occurred between them.

3. Spectrographic Studies.[11]—In repeated spectrographic analyses of the cocaine contained in the cerebrospinal fluid of dogs stained intensely with brilliant vital red (see section *C 2*), no alteration in the characteristic spectrum of cocaine was observed.

Examination of the spectrum of a 0.02 per cent solution of brilliant vital red exposed to an excess (0.1 per cent solution) of cocaine hydrochloride failed to reveal any significant shift in the characteristic bands of cocaine in either the visible or the ultraviolet range of the spectrum. Similarly, an analysis of the spectrum of cocaine hydrochloride, exposed to such concentrations of brilliant vital red as would not obscure its band at λ 2,750, showed no shift.

Summary.—The effective protection afforded by brilliant vital red against convulsive agents of widely different chemical structures suggested that a chemical neutralizing or bonding action between the dye and the drugs was not the mode of its protective action. Dialysis, electrophoresis and spectrographic studies conclusively confirmed this opinion.

C. Studies Suggesting That Brilliant Vital Red Alters the Permeability of the Endothelium and Thus Creates a Barrier Between the Central Nervous System and the Rest of the Body

1. Gross and Histologic Examinations.—Studies of the tissues of mice and dogs intensely stained with brilliant vital red showed the endothelium to be well stained, especially in certain localities, such as the liver, spleen, lymph glands and choroid plexus. Other tissues, such as the skin, connective tissue, epithelium of the tubules of the kidneys and dura mater, were stained in varying degrees of intensity.

Detailed studies on staining with brilliant vital red have been reported on by Evans[7] and Evans and Schulemann.[8] The results in the present studies, limited chiefly to the endothelium, are in full agreement with the observations of these authors. As presented in section II *B*, the central nervous system, aside from the vascular elements (choroid plexus and endothelium) and meningeal coverings, contained no trace of the dye.

Detailed studies of the choroid plexuses of mice and dogs showed the endothelium to be intensely stained, while the ependymal layer was not stained at all. Repeated examinations of the ependyma elsewhere revealed no trace of the dye.

These observations are consistent with the possibility that the dye alters the permeability of the endothelium and thus creates an effective barrier between the

11. These studies were made in collaboration with Louis Strait, Ph.D., of the department of physics, University of California.

central nervous system and the rest of the body. Indeed, in view of the subsequent studies, the element of doubt was largely removed.

2. Permeability of the Endothelium of the Hematoencephalic Barrier in Dogs with Experimental Epilepsy Before and After Staining with Brilliant Vital Red.—The following experiments were planned as a final test of the hypothesis, suggested by the previous studies, that brilliant vital red protects against epilepsy by lowering the permeability of the endothelium of the central nervous system (choroid plexus and elsewhere) to convulsive agents.

Methods.—A convulsive agent, such as cocaine, must reach the cerebral cortex to be effective.[12] If injected intravenously, a considerable portion of it would reach the central nervous system by way of the choroid plexus and cerebrospinal fluid.[13] Starting intraventricularly, the cerebrospinal fluid reaches the subarachnoid spaces in the cisterna magna. After intravenous injections of cocaine hydrochloride, therefore, drainage of the cerebrospinal fluid by cisternal puncture should effectively intercept some of the cocaine after it has entered the central nervous system. Since the endothelium and ependyma of the choroid plexus alone separate the blood and the cerebrospinal fluid, such a procedure, if properly standardized and controlled, might be used as a test of the permeability of the tissue to suitable convulsive agents. Alterations in permeability, if produced in the endothelium after staining with brilliant vital red (the ependyma is not stained with brilliant vital red), could be determined by repeated tests on the same animal under standard conditions before and after staining.

Spectrographic Determination of Cocaine Hydrochloride.[14]—Cocaine hydrochloride was selected as the convulsive agent because (1) its convulsive effect on animals as high in the phylogenetic scale as dogs has been shown to be primarily cortical,[12] (2) the convulsive dose is relatively large, which increases the chance of detecting it in the cerebrospinal fluid, and (3) it has a strong and characteristic absorption spectrum when dissolved in water, which makes its quantitative determination possible in extremely minute amounts.[15] Two adsorption bands, one centering at λ 2,750 and a somewhat stronger one centering approximately at λ 2,330, are characteristic of cocaine hydrochloride. Spectroscopic examination in the ultraviolet range was therefore necessary and was obtained by passing a beam of ultraviolet continuum from a water-cooled hydrogen discharge tube through the test solution contained in a cylindric quartz absorption cell, 5 cm. long and 20 mm. in diameter. The beam, after passing through the cell, was focused on the slit of a quartz spectrograph of 25 angstrom units per millimeter at λ 2,700 and photographed on no. I O ultraviolet Eastman plates, which are particularly sensitive to the ultraviolet rays.

Variations of blackening on the plates were registered quantitatively by the Zeiss recording microphotometer at the University of California. The difference

12. Feinberg, I.: Weitere Mittheilungen zur physiologischen Cocainwirkung, Berl. klin. Wchnschr. **24**:166-168, 1887. Morita, S.: Untersuchungen an grosshirnlösen Kaninchen: I. Das Verhalten der Blutzuckerkonzentration, Arch. f. exper. Path. u. Pharmakol. **78**:188-207, 1915.

13. Dandy, W., and Blackfan, K. D.: Internal Hydrocephalus: An Experimental, Clinical and Pathological Study, Am. J. Dis. Child. **8**:406-482 (Dec.) 1914; Internal Hydrocephalus: Second Paper, ibid. **14**:424-443 (Dec.) 1917.

14. The spectrographic studies were made in collaboration with Louis Strait, Ph.D., of the department of physics, University of California.

15. Castille, A.: Ultra-Violet Absorption Spectrum of the Alkaloids of the Tropeine Group, Bull. Acad. roy. de méd. de belgique **5**:193-200, 1925.

in height of the microphotometer curves for the test specimens and those for the control (a 0.04 normal solution of hydrochloric acid) is roughly a quantitative measure of the absorption of the cocaine hydrochloride at the wavelength selected for measurement. Exact measurements require corrections because the blackness of the plates does not vary directly with the intensity of absorption. Calibration of the characteristics of the plate (blackness versus intensity) was therefore necessary.

Preliminary spectrographic tests with cerebrospinal fluid showed absorption of all the incident wavelength below λ 2,800, and the bands characteristic of cocaine hydrochloride were completely obscured. The urea and uric acid contents of the cerebrospinal fluid were found to be responsible chiefly for the absorption below λ 2,800. A simple process of extraction was devised which took advantage of the great insolubility of these substances in chloroform, a solvent in which cocaine (not cocaine hydrochloride) is highly soluble. The specimen of cerebrospinal fluid was treated with 5 drops of concentrated ammonium hydroxide to insure complete transformation of all cocaine hydrochloride present into cocaine. The specimen was then shaken for ten minutes with twice its volume of chloroform, chemically pure. Salting-out effects of the cerebrospinal fluid were minimized by this single, uninterrupted extraction process. The layer of chloroform was next drawn off and evaporated at 37 C. The residue was redissolved in 5 cc. of a 0.04 normal solution of hydrochloric acid. The acid served to retransform the cocaine to cocaine hydrochloride, in which form it is highly soluble in water. The weak acid solution also proved to be a satisfactory solvent from the standpoint of the spectrographic technic. With this method, control extractions of cerebrospinal fluid showed only slightly more absorption than the solution of 0.04 normal hydrochloric acid alone, and the portions of the spectrum essential for the detection of cocaine hydrochloride were left relatively free. With standardization of the technic of extraction, the slight residual absorption was found to remain constant and therefore was of no importance in the determination of relative results. Since 15 cc. of cerebrospinal fluid was usually obtained for the extraction and the cocaine was finally redissolved in 5 cc. of the 0.04 normal solution of hydrochloric acid, a concentration three times that of the original concentration of cocaine hydrochloride was attained by this procedure. This, in addition to the efficiency of the extraction process, materially aided in the detection of cocaine in these studies.

Because of the limited amount of cocaine hydrochloride present in the specimens of cerebrospinal fluid (0.01 mg. or less), the stronger, λ 2,330, band usually was present alone. Photographs in numerous cases, however, showed the presence of the weaker, λ 2,750, band, thus establishing the use of the λ 2,330 band as satisfactory for quantitative determinations. Measurements of specimens for their relative content of cocaine hydrochloride before and after staining with brilliant vital red were based on the following consideration: If C represents the concentration of cocaine hydrochloride before staining and C′ that after staining, from application of Beer's law (certainly valid for weak solutions), it follows that

$$\frac{C}{C'} = \frac{K \log_{10} I}{K \log_{10} I'}$$

in which I and I′ are the relative intensities of light which is transmitted in the two cases. The method of photographic intensitometry permits the measurement of relative intensities by measuring blackness on a photographic plate and empirically establishing a relationship between blackness and intensity. The method of screens devised by Harrison[16] was employed to calibrate the photographic emulsion for determining this relationship.

16. Harrison, G. R.: Instruments and Methods Used for Measuring Spectral Light Intensities, J. Optic. Soc. America **19**:267-315, 1929.

Animal Experiments.—Because the method involved repeated cisternal punctures on the same animal and the drainage of considerable amounts of cerebrospinal fluid to facilitate the detection of the convulsive agent, large dogs were used in the study. The dogs were maintained under favorable housing conditions on a special diet rich in protein and vitamins. A diet somewhat low in fat and relatively high in carbohydrate, without restriction of fluids, was given throughout the experimental period to avoid any tendency to ketosis or dehydration. Tests were performed only once a week to allow full recovery of the animals and insure that the tests were made under good and comparable conditions of weight and health.

The experimental procedure was standardized as follows: The dose of cocaine hydrochloride which would produce convulsions when injected intravenously was carefully determined for each animal, protection being immediately afforded by the injection intravenously of 28 mg. of pentobarbital sodium per kilogram of body weight. Subsequent tests were performed with doses of cocaine hydrochloride from 0.5 to 1.5 mg. in excess of the convulsive dose; the dose in each animal, however, was constant in all the tests. This higher dose insured tests in the convulsive ranges for the animals, in spite of any tendency for them to acquire tolerance to the cocaine with repeated tests. The higher dose also increased the chances of successful and accurate detection of the cocaine in the specimens of cerebrospinal fluid. Injections of still higher doses were not attempted, since the margin of safety between convulsive and fatal doses is relatively slight in the case of cocaine.

The tests were conducted with the animal under anesthesia obtained by the injection intravenously of 28 mg. of pentobarbital sodium per kilogram of body weight. Cisternal puncture under aseptic conditions by means of a no. 19 gage lumbar puncture needle was performed with the dog lying on the right side on a special table, the body tilted head down at an angle of 25 degrees and the head flexed on the chest and rotated laterally to afford maximum drainage of cerebrospinal fluid. A cisternal tap with free drainage of clear fluid was obtained before proceeding further. The test dose of cocaine hydrochloride in a 5 per cent solution was next injected intravenously, time being recorded at the beginning and the end of the injection. Ten seconds after the injection, or at selected later periods, the drainage of cerebrospinal fluid was started by removal of the stilet from the needle. The rate of flow was recorded by counting the drops for each ten seconds throughout the test period. When the rate fell to 8 or 10 drops per ten seconds, air was injected to increase the cerebrospinal fluid pressure and allow greater drainage of the fluid. By this means the rate of flow could be roughly controlled and the total period of collection kept constant at three minutes. Fifteen cubic centimeters of cerebrospinal fluid was obtained in most instances, but in some of the final tests a tendency to slower rates of flow and poorer collections was noted, for which it was not always possible to compensate by the technic described. The interpretation in these instances was necessarily modified.

Two or more tests were performed in this manner prior to staining with brilliant vital red, and from five to seven tests were performed on each animal after the staining, the dose, conditions and methods before and after staining being identical.

Repeated early tests (collection of cerebrospinal fluid between ten and one hundred and ninety seconds after injection of the cocaine hydrochloride) were made to insure comparable tests before and after staining and as a check on the variations to be found from one test to another, made by the same technic and under the same conditions. Late tests (collections of cerebrospinal fluid between

three and six minutes, six and nine minutes and nine and twelve minutes after the injection of cocaine) were performed, particularly after staining with brilliant vital red, as a check on any possible compensatory shift in the quantity of cocaine appearing at later periods.

Because the dogs might conceivably have acquired tolerance to cocaine hydrochloride as a result of the repeated tests, which would be of considerable significance in interpretation of the results obtained in the study, the convulsive threshold was again determined for each animal at the end of the series of tests.

Technic of Staining with Brilliant Vital Red.—Staining with brilliant vital red was accomplished by seven or eight daily injections intravenously of 30 cc. of a 1 per cent sterilized solution of the dye. A total of 2.1 or 2.4 Gm. of the dye was thus injected, which resulted in a moderately bright pink stain of the skin, mucous membranes and blood vessels of the conjunctiva. Two injections were given in the interval of one week between tests, to maintain the staining effect. Two days were allowed to elapse after the final injection of brilliant vital red before any test was made.

Results.—By a series of preliminary spectrographic studies based chiefly on the specimens of cerebrospinal fluid obtained in 60 cisternal punctures on 18 dogs, the procedure was perfected and standardized. Spectrograms, based on 30 tests on 6 dogs, were obtained, with use of the perfected technic. Of these, the results in only 3 dogs (21 spectrograms) fulfilled the critical criteria demanded in the study. The observations in these 3 cases are recorded in detail in table 2. Although the results are presented only in these 3 cases, it should be said that the data accumulated in both the preliminary and the final studies which are not recorded here were essentially consistent (to the extent to which they were complete) with the results reported. This fact was thought to be particularly significant from the standpoint of establishing the reliability and accuracy of the method.

The experience with 1 animal (dog 239), although representing a violation of the technic, is worthy of mention because it corrobrates from another angle the reliability of the method, as well as the relative protection afforded by brilliant vital red. Two tests were made satisfactorily, prior to staining, an intravenous dose of 15 mg. of cocaine hydrochloride per kilogram of body weight being used. By mistake, this dog was stained with 2.4 Gm. (eight injections) of vital red (H. R. Ehrlich), instead of brilliant vital red (Evans). In the next test, although the conditions and dose of cocaine hydrochloride were identical with those before staining, the animal died. The spectrogram of the specimen of cerebrospinal fluid revealed an unusual amount of cocaine hydrochloride, more than twice that obtained in the control tests. This result reminds one of the observations of Ducrot and Gautrelet[17] and Stern[18] and Stern and Gautier,[19] who reported the

17. Ducrot, R., and Gautrelet, J.: Le liquide céphalo-rachidien au cours de l'ictére expérimental, Compt. rend. Soc. de biol. **58**:160-161, 1905; Présence des pigments biliaires dans le liquide céphalo-rachidien aprés suppression physiologique des plexus choiroïdes, ibid. **58**:161-162, 1905.

18. Stern, L.: Le liquide céphalo-rachidien au point de vue de ses rapports avec la circulation sanguine et avec les éléments nerveux de l'axe cérébrospinal, Schweiz. Arch. f. Neurol. u. Psychiat. **8**:215-232, 1921.

19. Stern, L., and Gautier, R.: Recherches sur le liquide céphalo-rachidien: I. Les rapports entre le liquide céphalo-rachidien et la circulation sanguine, Arch. internat. de physiol. **17**:138-191, 1921; II. Les rapports entre le liquide céphalo-rachidien et les éléments nerveux de l'axe cérébrospinal, ibid. **17**:391-448, 1922.

TABLE 2.—*Studies on Endothelial Permeability in Experimental Epilepsy*

Dog	Before or After Staining with Brilliant Vital Red	Intravenous Dose of Cocaine Hydrochloride, Mg. per Kg. of Body Weight	Interval Between Intravenous Injection of Cocaine and Collection of Cerebrospinal Fluid	Volume of Content of Cerebrospinal Fluid Collected, Cc.	Quantitative Determination of Content of Cerebrospinal Fluid; Difference in Cocaine Hydrochloride* (C) Before and (C^1) After Staining with Brilliant Vital Red*			Decrease of Cocaine Hydrochloride in Specimens of Cerebrospinal Fluid (10 to 190 Sec. After Injection of Cocaine Hydrochloride) After Staining with Brilliant Vital Red		
					Measurement	Estimated Correction	Average† Measurement	Lowest, Percentage	Highest, Percentage	Average, Percentage
215. Convulsion with 13.5 mg. per Kg.	Before	15	10-190 sec.	13	1.22	....	....			
		14	10-190 sec.	13	1.35	1.35	1.35			
	After	14	10-190 sec.	13	0.97	0.97				
		14	10-190 sec.	10	0.58	0.75		28	44	36
		14	3-6 min.	12	0.59	0.64	0.86			
		14	3-6 min.	12	0.61	0.66				
		14	6-9 min.	11.5	0.44	0.50				
296. Convulsion with 10.5 mg. per Kg.	Before	12	10-190 sec.	14	1.45	1.45				
		12	10-190 sec.	15	1.33	1.24	1.34			
		12	3-6 min.	15	1.43	1.33				
	After	12	10-190 sec.	15	0.85	0.79		36	74	57
		12	10-190 sec.	12	0.32	0.37				
		12	3-6 min.	14	0.75	0.75	0.58			
		12	6-9 min.	13	0.52	0.56				
		12	9-12 min.	12	0.50	0.58				
322. Convulsion with 10 mg. per Kg.	Before	10.5	10-190 sec.	15	0.92	0.92	0.91			
		10.5	10-190 sec.	15	0.91	0.91				
	After	10.5	10-190 sec.	14	0.42	0.65		23	57	36
		10.5	10-190 sec.	15	0.70	0.70	0.58			
		10.5	10-190 sec.	15	0.40	0.40				
		10.5	3-6 min.	15	0.70	0.70				

* C and C^1 were determined by measurements of intensity and are proportional to the concentrations of the solutions of cocaine hydrochloride before and after staining with brilliant vital red, respectively (see text).

† Variations in collected volumes of cerebrospinal fluid were arbitrarily corrected and reduced to a comparative basis.

appearance of bile and iron compounds, respectively, in the cerebrospinal fluid following the injection of methylene violet, which injured the choroid plexus and suppressed its "barrier" function.

It will be seen (table 2) that the results in individual and comparable tests (identical periods of collection and volumes of cerebrospinal fluid collected) before and after staining with brilliant vital red are essentially the same as the average values for similar periods of collection, corrected for variations of volume. Also, since the values for different periods of collection for the same animal are not strikingly different, the same statement may be made in general for all the results; i. e., regardless of the type of analysis, the results obtained in each case consistently showed a marked drop in the concentration of cocaine entering the cerebrospinal fluid after staining with brilliant vital red as compared with the concentrations of the drug entering the cerebrospinal fluid prior to staining. The average drop for all dogs was approximately 43 per cent, the minimal calculated drop (the lowest value for cocaine prior to staining as compared with the highest value after staining in the same animal) being 23 per cent, for dog 322. Since control studies indicated that the spectrographic technic was accurate to within 10 per cent, the magnitude and consistency of these results seemed to justify the conclusion that the phenomenon observed was real and significant.

The final tests for the convulsive threshold of each of the 3 animals showed that the thresholds for cocaine hydrochloride had not been raised above the respective test doses used. The results, therefore, are not to be explained in terms of tolerance. Also, since the animals were protected by pentobarbital, the interpretation of the results is not complicated by any effects which might be secondary to convulsive seizures.

Interpretation.—These studies indicate, first, that the endothelium may be an effective barrier between the central nervous system and the rest of the body and, second, that alterations in the permeability of this barrier may be an important factor in epilepsy.

Two interpretations, however, are possible in explanation of the results obtained in the cocaine studies on dogs (section *C 2*). An alteration in the rate of transfer of water through the endothelium, as well as the more obvious explanation, that of a specific alteration in the permeability of the endothelium to cocaine, might account for the results obtained. The first concept must be considered, inasmuch as water is the necessary vehicle for cocaine and a reduction in the rate at which water could pass through the endothelium would correspondingly reduce the amount of drug being transmitted over any given period.

Although either explanation depends on an alteration in the semipermeable characteristics of the endothelium, it is important to distinguish between them. Lowering of the rate of water transfer (aside from reducing the amount of convulsive agent reaching the central nervous system in animals with experimental epilepsy) might be effective in the control of human epilepsy, merely by inhibiting hydration and its effects in the central nervous system. This possibility, if proved, emphasizes the importance of the water balance in the convulsive state.

On the other hand, if the permeability of the endothelium were specifically altered for cocaine (and the other convulsive drugs), tissue permeability, with all the implications this conveys (see "General Comment"), would be established as a factor of importance in epilepsy.

To settle this question of interpretation, raised by the preceding studies (section *C 2*), the following methods were devised, with the object of determining the rate of water transfer through the endothelium of the central nervous system, before and after staining with brilliant vital red.

Further Experiments on Water Transfer.—(1) The lumen of a cisternal puncture needle may be considered to be roughly constant, in any one animal, in relation to the cross section of the subarachnoid channel for the circulation of cerebrospinal fluid. Variations in the rate of formation of cerebrospinal fluid, therefore, would be reflected in the rate of its flow through the subarachnoid channels and, proportionately, in the rate of drainage from the needle. This, of course, is true only after the reservoir capacity of the subarachnoid spaces has been exhausted, i. e., after the initial drainage of cerebrospinal fluid has diminished to a steady, slow drip. Determinations of average rates of cisternal drainage over prolonged periods under standard conditions might therefore be taken as a fairly accurate indication of the rate of formation of cerebrospinal fluid. Since the rate at which water is transferred through the endothelium which is concerned with the formation of cerebrospinal fluid necessarily determines the rate of formation of cerebrospinal fluid, observations on cisternal drainage, under the conditions considered, should be a relative and fairly accurate measure of this rate of formation.

(2) Of the various constituents of cerebrospinal fluid, sodium alone is maintained at a concentration identical with that found in the blood.[20] Alterations in the concentration of sodium in the blood are quickly reflected in a corresponding change in the concentration of sodium in the cerebrospinal fluid.[21] It seems safe to conclude from these facts that the permeability of the endothelium concerned with the formation of cerebrospinal fluid exerts no appreciable inhibitory effect on the movements or passage of sodium. Sodium may be rendered radioactive[22] without affecting its chemical characteristics,[23] and the measurement of the rate at which radioactive sodium passes from the blood into the cerebrospinal fluid may be determined with considerable accuracy. Therefore, because water is the

20. McVicar, C. S., and Ross, H.: The Sodium and Potassium Content of Blood Serum in Various Diseases and of the Cerebrospinal Fluid in Proved and Suspected Syphilis, J. Lab. & Clin. Med. **9**:87-91, 1923.

21. Dailey, M. E.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: The Distribution of Sodium Between Cerebrospinal Fluid and Blood Serum, J. Biol. Chem. **93**:5-15, 1931.

22. Lawrence, E. O.: Radioactive Sodium Produced by Deuton Bombardment, Phys. Rev. **46**:746, 1934. Lawrence, E. O., and Cooksey, D.: On the Apparatus for the Multiple Acceleration of Light Ions to High Speeds, ibid. **50**: 1131-1140, 1936.

23. Hamilton, J. G.: The Rates of Absorption of Radio-Sodium in Normal Human Subjects, Proc. Nat. Acad. Sc. **23**:521-527, 1937.

necessary vehicle for sodium and the quantitative relation between them is closely regulated by the physiologic forces which maintain isotonicity, the measurement of the rate at which radioactive sodium passes from the blood into the cerebrospinal fluid is also a measure of the rate of water transfer through the endothelium of the hematoencephalic barrier.

If variations in the rate of water transfer through the endothelium of the hematoencephalic barrier are produced by staining with brilliant vital red, they should be detected by such methods.

Because the second method, involving radioactive sodium, also required cisternal drainage and collection of cerebrospinal fluid over prolonged periods, it was possible to utilize both technics simultaneously. The studies were made on dogs, the test being conducted as follows: The dogs were anesthetized with pentobarbital sodium, 28 mg. per kilogram of body weight being injected intravenously, and extra injections were given as necessary to maintain the anesthesia throughout the test period. The dogs, lying on the right side, were strapped to a table tilted at an angle of 25 degrees, with the head end down. Cisternal punctures were performed with aseptic precautions, and the reservoirs of cerebrospinal fluid were allowed to drain freely. When the rate of drainage had become steady (usually within from forty-five to fifty-five minutes after the cisternal tap), from 5 to 15 cc. of an isotonic solution of sodium chloride containing radioactive sodium was injected intravenously. The volume injected depended on the strength of the solution, which was always determined in advance. Collection of the cerebrospinal fluid was started at the time of the injection of the radioactive solution and continued for from two to three and a half hours. Ten minute specimens were obtained during the first half-hour, fifteen minute specimens during the next half-hour and twenty minute specimens after the first hour. Occasional specimens of blood were taken throughout the test period and were measured for radioactivity as a check on the rate of dissipation of the injected radioactive sodium.

Prof. E. O. Lawrence prepared the radioactive sodium.

Measurements of radioactivity [24] were made with the use of a Lauritsen electroscope.

Two tests were performed on each animal, after which each was stained with brilliant vital red in the manner described previously (section *C 2*). From one to three tests were performed after the staining. The technic and conditions of the test were standardized so that, except for the one variable of staining with brilliant vital red, all tests were comparable. The interval between tests in any animal was at least one week. The diet and care of the animals were the same as described in section *C 2*.

Results: A satisfactory series of tests was completed on 3 dogs, 1 of which (dog 215) was used in the previous study on cocaine (section *C 2*), several months previously. Because of the long interval between the two studies, this dog had completely lost its color (sclera, mucous membranes and skin) and therefore was considered suitable for the present study. The other 2 animals had never been stained with brilliant vital red.

The volume flow of the draining cerebrospinal fluid was computed on the basis of the average volume obtained per five minutes throughout the various periods of collection. Obstruction to the free drainage of the cerebrospinal fluid,

24. The studies on radioactive sodium were made in collaboration with Mr. Waldo Cohn, of the department of biochemistry, University of California Medical School.

which occasionally occurred, was readily detected by this means. The average flow per five minutes, throughout the entire period of free drainage, was then computed. The results obtained in individual tests before and after staining with brilliant vital red are presented in table 3. No alterations occurred which could be ascribed to the effect of the dye.

The measurement of radioactivity was computed on the basis of the number of units of radioactivity per cubic centimeter of cerebrospinal fluid collected for each 10^5 units of radioactive sodium injected intravenously. By plotting these values on the ordinates and the time of collection on the abscissas, the rate at which radioactive sodium enters the cerebrospinal fluid is shown graphically for each animal in the various tests before (solid) and after (broken) staining with the brilliant vital red (figure). It is evident from these data that the dye has no effect on the rate at which sodium enters the cerebrospinal fluid.

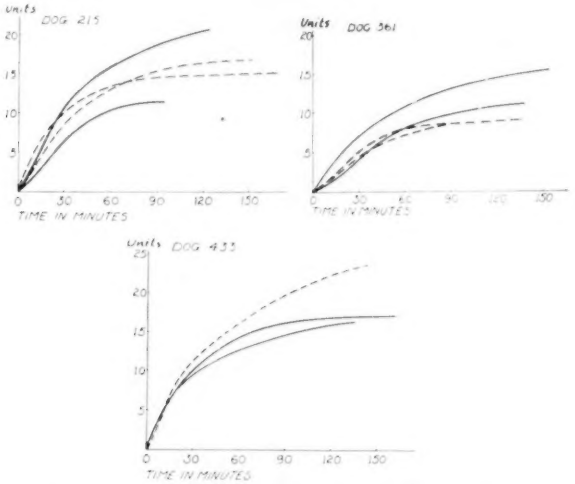
TABLE 3.—*Average Flow of Cerebrospinal Fluid per Five Minute Period After Cisternal Puncture*

Dog	Treatment with Brilliant Vital Red	Time of Period of Collection After Cisternal Puncture	Average Flow of Fluid per Five Minute Period, Cc.
215	Before	54 min. to 2 hr. and 9 min.	0.272
(21 Kg.)		1 hr. and 4 min. to 2 hr. and 56 min.	0.173
	After	49 min. to 3 hr. and 29 min.	0.227
		54 min. to 1 hr. and 24 min.	0.187
		45 min. to 3 hr. and 5 min.	0.194
433	Before	50 min. to 3 hr.	0.317
(20.6 Kg.)		54 min. to 3 hr. and 14 min.	0.329
	After	1 hr. and 45 min. to 2 hr. and 35 min.	0.325
261	Before	52 min. to 3 hr. and 12 min.	0.28
(21.6 Kg.)		1 hr. and 10 min. to 3 hr. and 10 min.	0.306
	After	55 min. to 3 hr. and 5 min.	0.346
		50 min. to 1 hr. and 30 min.	0.37

The negative results obtained by both methods seem to indicate conclusively that the rate of water transfer through the endothelium, concerned with the formation of cerebrospinal fluid, is not altered by the staining effect of brilliant vital red.

Summary.—Histologic studies on animals stained with brilliant vital red suggested, in view of the refutation of other hypotheses, that the dye afforded protection in experimental epilepsy by rendering the endothelium of the hematoencephalic barrier relatively impermeable to the passage of convulsive agents. This possibility was directly confirmed by spectrographic determinations of the amount of cocaine entering the cerebrospinal fluid of dogs after its intravenous injection and by comparison of the results in the same animal under standard conditions before and after staining with brilliant vital red.

Further studies ruled out the possibility that the dye altered the rate of water transfer through the endothelium (concerned with the formation of cerebrospinal fluid), a possibility which might have produced the marked and consistent drop observed in the amount of cocaine entering the cerebrospinal fluid after staining with brilliant vital red. The conclusion was reached that brilliant vital red produces a specific alteration in the permeability of the endothelium of the central nervous system (choroid plexus and elsewhere) to cocaine hydrochloride and, presumably, to other convulsive agents. It was further concluded that the endothelium may be an effective barrier between the central nervous system and the rest of the body and that alterations in the permeability of this barrier may be an important factor in epilepsy.



Rate of transfer of water through the endothelium of the hematoencephalic barrier, as measured by the rate at which radioactive sodium enters the cerebrospinal fluid of dogs after intravenous injection. Solid lines indicate studies made of controls before staining with brilliant vital red; broken lines, studies made after staining with brilliant vital red.

The amount of radioactive sodium is measured on the basis of the number of units per cubic centimeter of cerebrospinal fluid collected for each 10^5 units of radioactive sodium injected.

GENERAL COMMENT

In experimental epilepsy, in which it was shown that brilliant vital red protects by rendering the endothelium of the central nervous system relatively impermeable to convulsive drugs, the relationship of toxin, permeability of the "barrier" and seizures is evident. That an analogous situation exists in human epilepsy is not entirely clear. In production of human epilepsy, for example, the counterpart of the experimental

convulsive agents is by no means obvious. The importance of the endothelium as a barrier between the central nervous system and the rest of the body is also obscure. The fact that brilliant vital red benefits patients suffering from convulsive states is, however, strong evidence in favor of such a relationship. Furthermore, certain facts in connection with human epilepsy support the conception of "toxic" seizures and suggest the character of the convulsive toxins involved. The deleterious effect of infectious processes on epileptic persons, for example, is in keeping with this concept. Systemic toxemias of infectious origin, and infectious processes of the central nervous system in particular, exaggerate the convulsive state of epileptic patients and, in fact, may produce seizures in nonepileptic persons. The particular effectiveness of infections of the central nervous system not only confirms the possibility of "toxic fits" but also suggests the great importance of the endothelial "barrier" in protecting the central nervous system from toxemias of systemic origin. Noninfectious toxemias (such as uremia, eclampsia and the toxemias due to alcohol and lead) likewise may be factors of etiologic importance in epilepsy.

Indisputable evidence of the existence of a barrier between the central nervous system and the rest of the body is found in the fact that, with the exception of sodium, substances common to both the cerebrospinal fluid and the blood are maintained at different levels of concentration and that proteins are almost completely excluded from the cerebrospinal fluid. Considerable experimental and clinical evidence has been accumulated to show that this "barrier" plays a vital role in the metabolism of the central nervous system.[25] Also, it has been found to have a protective function.[26] It has been shown by clinicopathologic and experimental studies that when the choroid plexus is injured the function of the "barrier" is impaired or abolished with respect to certain dyes, bile pigments and iron compounds. Such impairment in the function of the "barrier" might exaggerate the effectiveness of systemic toxemias. Toxicity, therefore, is a relative term as far as the central nervous system is concerned, and, in determining it, the condition of the endothelial "barrier" (its permeability to the specific toxin) is as important as the severity of the toxemia. Relatively severe systemic toxemias may have little central effect provided the "barrier" is effective

25. Stern.[18] Stern and Gautier.[19]

26. Schmorl, G.: Untersuchungen über Icterus neonatorum, Zentralbl. f. Gynäk. **26**:1049-1051, 1902. Cestan, R.; Riser, and Pérès, M.: Physio-pathologie des ventricules cérébraux dans la syphilis nerveuse, Ann. de méd. **15**:201-222, 1924. Stern, L.: Modification fonctionnelle de la barrière hémato-encéphalique dans quelques conditions pathologiques, Schweiz. med. Wchnschr. **53**:502, 1923.

for them. On the other hand, relatively slight toxemias may become important if the permeability of the "barrier" to them is abnormally increased.

The effectiveness of brilliant vital red in "nontoxic" epileptic persons suggests that this relationship is significant in the case of epilepsy, that is, that abnormally increased permeability of the endothelium may be as important an etiologic factor in the production of seizures as abnormal toxic states. Such appears to be the explanation for the increased susceptibility of epileptic women at the premenstrual and menstrual periods. Heilig and Hoff [27] and Benda [28] showed that this stage of the menstrual cycle is associated with an increased permeability of the endothelium to uranin (fluorescein sodium), and bromine respectively. Peterson and Milles [29] observed the same phenomenon in the skin of women just before and at the time of the menses.

The relation of allergy to epilepsy might be explained in the same way. Petersen and Müller [30] found that anaphylactic shock is associated with an increased vascular permeability to proteins, while Stern, Kassil and Lokschina [31] reported that there was abnormal permeability to colloids of the hematoencephalic barrier in the presence of anaphylactic shock.

The minimal toxemias (not due to infections and such conditions, as considered previously) which are effective in these conditions might be aberrant tendencies of normal metabolism, such as borderline hypoglycemic states, the alkalosis of hyperventilation, produced subconsciously in times of emotional disturbances, and even the excessive accumulation of fatigue products.

Numerous efforts have been made to determine alterations in the permeability of the hematoencephalic barrier in epilepsy as well as in other conditions. Redlich, Pötzl and Hess [32] found no difference in the readiness with which ingested substances, such as methylthionine chloride U. S. P. (methylene blue), sodium salicylate, bromine and acetone,

27. Heilig, R., and Hoff, H.: Menstruation und Liquor, Klin. Wchnschr. **3**: 2049-2051, 1924.

28. Benda, R.: Das reticulo-endotheliale System in der Schwangerschaft: Eine experimentell-klinische Studie, Berlin, Urban & Schwarzenberg, 1927.

29. Petersen, W. F., and Milles, G.: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch. Int. Med. **38**:730-735 (Dec.) 1926.

30. Petersen, W. F., and Müller, E. F.: Ueber Aenderungen in der Permeabilität nach Insulin, Ztschr. f. d. ges. exper. Med. **54**:415-438, 1927.

31. Stern, L.; Kassil, G. N., and Lokschina, E. S.: Effet de l'anaphylaxie sur le fonctionnement de la barrière hémato-encéphalique, Compt. rend. Soc. de biol. **99**:451-452, 1928.

32. Redlich, E.; Pötzl, O., and Hess, L.: Untersuchungen über das Verhalten des Liquor cerebrospinalis bei der Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **2**:715-725, 1910.

appeared in the cerebrospinal fluid of epileptic persons and of control subjects. Other workers obtained similar negative results with uranin and bromine. These studies were well summarized by Katzenelbogen,[33] who has done considerable work on the bromide permeability test in cases of epilepsy. The obvious shortcoming of these studies lies in the fact that their significance is limited to the particular agent used for testing permeability. The results obtained with bromine in cases of epilepsy, for example, have no significance with respect to those which might be obtained with the use of epileptogenous agents. Permeability involves a selective specificity for the transmission, or failure of transmission, of metabolites and drugs in solution. Consequently, negative observations of the sort referred to have no significance with respect to the validity of positive observations, such as are recorded in this study.

Direct experimental efforts to demonstrate convulsive toxins in the blood of epileptic persons[34] are noteworthy if confirmed. Since convulsive toxins are toxic only to the extent they can penetrate the "barrier" and reach the brain, such studies, based on the injection of material from one person into another, are difficult to evaluate. A toxin which is effective in one person may well prove ineffective in another whose "barrier" tissues are relatively more impermeable to the toxin. This approach to the problem, therefore, is necessarily limited, in that it fails to consider tissue permeability as a factor in epilepsy.

As a result of such considerations it seems safe to conclude that "toxic" seizures and a "barrier," dependent on the permeability of the endothelium of the central nervous system, are probably important factors in human epilepsy.

Also worthy of note is the experimental work[35] which indicates that the function of the "barrier" is impaired by injuries to the brain.

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33. Katzenelbogen, S.: Examination of the Function of the Barrier Between Blood and Cerebrospinal Fluid, in The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935, chap. 16.

34. Trevisanello, C.: Untersuchungen über das Blutserum und die Cerebrospinalflüssigkeit von Epileptikern, Centralbl. f. Bakt. (Abt. 1) **69**:163-166, 1913. Speransky, A.: La congélation des tissus: Procédé d'obtention de l'auto-neurotoxine et d'autres autotoxines cellulaires, Ann. Inst. Pasteur **40**:213-231, 1926; L'influence du liquide céphalo-rachidien sur l'évolution des processus physiologiques et pathologiques du cerveau, ibid. **40**:755-786, 1926. Buscaino, V. M., and Longo, V.: Ricerche sperimentali sulla tossicita del sangue degli epilettici: Dati neurologici, Riv. di pat. nerv. **48**:682-685, 1936.

35. (*a*) Barbour, H. G., and Abel, J. J.: Tetanic Convulsions in Frogs Produced by Acid Fuchsin, and Their Relation to the Problem of Inhibition in the Central Nervous System, J. Pharmacol. & Exper. Therap. **2**:167-199, 1910. (*b*) Abel, J. J.: On the Action of Drugs and the Function of the Anterior Lymph Hearts in Cardiectomized Frogs, ibid. **3**:581-608, 1912. (*c*) Sauerbruch, F.:

(Footnote continued on next page)

Although certain of these observations might be interpreted as indicating failure of the "barrier" secondary to direct injury of the endothelium, the studies of Sauerbruch,[35c] MacCurdy and Evans [6] and Dandy and Elman [35f] can be interpreted only in terms of increased permeability of the endothelium concerned with the formation of cerebrospinal fluid. Furthermore, the studies of Sauerbruch [35c] and Dandy and Elman [35f] have indicated that the effect persists over a considerable period and therefore is not associated with the period of acute injury alone. It is conceivable that such a factor may be of etiologic significance in the convulsive states, seen clinically, which are associated with postinfectious (meningitis, encephalitis and abscess of the brain) and post-traumatic conditions of the central nervous system.

Although considerable evidence may thus be adduced to support the hypothesis that systemic toxemias and endothelial permeability are factors of importance in human epilepsy, as they have been shown to be in the case of experimental epilepsy, it is not meant to imply that this mechanism is the primary etiologic factor in epilepsy. Some fundamental disturbance in cellular metabolism of the cerebral cortex, such as anoxemia, appears to be the final condition necessary for production of the convulsive state. Systemic toxemias, therefore, are toxic in a convulsive sense only to the extent that they tend to produce the final intracellular condition necessary for the cellular "explosions" typical of epilepsy. Endothelial permeability, correspondingly, is a factor of etiologic importance in epilepsy to the extent that it forms a barrier which protects the central nervous system against such convulsive toxins.

It is conceivable, and indeed suggested by these results, that the cell membranes of the cortical tissue may form a second, and even more important, barrier. This barrier would be effective against toxemias originating in the central nervous system as well as those of systemic origin. Also, because this barrier would necessarily control directly the transfer of metabolites concerned with the oxygenation and nutrition of the cell, as well as the elimination of the waste products of cellular metabolism, it may well play a vital role in the establishment of the final intracellular condition necessary for the production of the convulsive

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Experimentelle Studien über die Entstehung der Epilepsie, Verhandl. d. deutsch. Gesellsch. f. Chir. **42**:144-149, 1913. (*d*) Rachmanow, A.: Beiträge zur vitalen Färbung des Zentralnervensystems, Folia neuro-biol. **7**:750-771, 1913. (*e*) Syz, H. C.: On the Entrance of Convulsant Dyes into the Substance of the Brain and Spinal Cord After an Injury to These Structures, J. Pharmacol. & Exper. Therap. **21**:263-290, 1923. (*f*) Dandy, W. E., and Elman, R.: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. **36**:40-49, 1925. (*g*) Mendel, W.: Versuche über das Eindringen intravenös injizierten Trypanblaus in das künstlich verletzte Grosshirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:148-162, 1928. (*h*) MacCurdy and Evans.[6]

state. Such various mechanisms as hydration, alkalosis and anoxemia, known to favor the production of seizures, may operate on this "barrier" to influence the establishment of the fundamental intracellular condition properly termed the convulsive state.

The work of Spiegel and Spiegel-Adolf [36] tends to support this conception. Using indirect electrical methods, they showed that conditions which favor the production of seizures (anoxemia and alkalosis, for example) are associated with an increase in the permeability of the cortical tissue. Although such evidence is not conclusive, it is extremely suggestive, especially when considered in the light of the direct evidence obtained in this study showing the importance in the production of epilepsy of the permeability of another barrier.

CONCLUSIONS

1. The endothelium concerned with the formation of cerebrospinal fluid forms an effective protective barrier to the central nervous system.

2. In animals with experimental epilepsy brilliant vital red renders this "barrier" relatively impermeable to the passage of cocaine hydrochloride. The same effect presumably holds for the other convulsive agents (picrotoxin, strychnine, camphor and triphenylphosphite) tested in connection with brilliant vital red.

3. Brilliant vital red affords protection in cases of human epilepsy. This fact, in addition to various other considerations which are discussed, affords strong evidence in support of the hypothesis that "convulsive toxins" and the endothelium of the hematoencephalic barrier are factors of etiologic importance in human epilepsy and that the relation between them is analogous to that demonstrated in experimental epilepsy.

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36. Spiegel, E., and Spiegel-Adolf, M.: Physiochemical Mechanisms in Convulsive Reactivity, Proc. Soc. Exper. Biol. & Med. **34**:799-800, 1936; Fundamental Effects of Epileptogenous Agents upon the Central Nervous System, Am. J. Psychiat. **92**:1145-1168, 1936.

SKIN AND BODY TEMPERATURES OF SCHIZOPHRENIC AND NORMAL SUBJECTS UNDER VARYING ENVIRONMENTAL CONDITIONS

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Investigations of the physiologic concomitants of the schizophrenic psychosis have suggested a certain degree of dysfunction of the autonomic nervous system.[1] It has been difficult, however, to obtain unequivocal experimental data by which to determine the matter. Since the autonomic nervous system controls the responsiveness of the thermoregulating mechanisms, it has been attempted in the following series of studies to determine the state of the former through the physiologic reactions of the latter.

There have been reported heretofore no accurate studies under controlled conditions of skin temperature in schizophrenic subjects. It is the general clinical impression that subjects suffering from this psychosis have cold and clammy extremities. Finkelman and Stephens [2] reported a greater fall in body temperature in schizophrenic than in nonpsychotic subjects on exposure to cold baths. Gottlieb and Linder [3] found a greater increase in body temperature in schizophrenic than in normal persons after exposure to warm air. Cameron [4] noted that the body temperature of schizophrenic subjects is lower than that of nonschizophrenic psychotic subjects and that the schizophrenic persons have a greater rise in body temperature after exposure to cold baths and a lesser rise after exposure to hot baths than the other group.

From the Research Service of the Worcester State Hospital.

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1. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1933.

2. Finkelman, I., and Stephens, W. M.: Heat Regulation in Dementia Praecox: Reactions of Patients with Dementia Praecox to Cold, J. Neurol. & Psychopath. **16**:321, 1936.

3. Gottlieb, J. S., and Linder, F. E.: Body Temperatures of Persons with Schizophrenia and of Normal Subjects: Effect of Changes in Environmental Temperature, Arch. Neurol. & Psychiat. **33**:775 (April) 1935.

4. Cameron, D. E.: Heat Production and Heat Control in the Schizophrenic Reaction, Arch. Neurol. & Psychiat. **32**:704 (Oct.) 1934.

MATERIAL AND METHODS

The subjects studied in this investigation were healthy men and schizophrenic patients. The latter represented all varieties of the schizophrenic syndrome and had been hospitalized for years. Thus, the subjects represented the chronic type of the disease. The normal and the schizophrenic subjects were approximately matched for height and weight and were studied in pairs in order to insure a similarity of environmental conditions in the two groups.

All the studies were made in an air-conditioned laboratory in which adequate control of the environmental factors could be attained. In this room the temperature could be controlled through a range of from 10 to 50 C. (50 to 122 F.); the degree of relative humidity could be regulated from 20 to 90 per cent, and the air velocity could be varied to a marked extent. Each factor could be changed independently of the other two.

The subjects, in a fasting state, were taken directly from bed to the laboratory. On arrival they disrobed completely and lay down on coarsely woven cane beds with no coverings. Their bodies were thus completely exposed to the environmental conditions. Skin and rectal temperatures were determined by means of thermocouples. Measurements of skin temperature were made on the forehead and nine pairs of areas on symmetric portions of the body surface, namely, the chest, abdomen, upper and lower parts of the arm, thenar eminence, tip of the middle finger, thigh, lower part of the leg and instep. A preliminary study [5] on the bilateral symmetry of skin temperatures showed a high degree of similarity between the temperatures of symmetric areas, so that, for the sake of simplicity, the data pertaining to one side only—the right—are presented.

RESULTS

The studies described in this paper deal with the changes in skin and rectal temperatures under varying environmental conditions, ranging from 15 to 44 C. (59 to 110.2 F.). In this way judgment can be made of the efficiency of the vasoconstricting and vasodilating mechanisms of the schizophrenic subject as compared with that of the normal person. These observations were made at a constant low relative humidity in order to permit evaluation of the effects of variation in the temperature alone. In addition, studies were made at constant levels of temperature, with humidity as the variable, in the hope of obtaining information on the sweating mechanisms. The investigations were spread over the winter and spring months, so that seasonal variations as a factor in adaptation could be ruled out.

The effects of cold air on the skin temperature will be discussed first. Three groups of 10 normal control subjects and the matched schizophrenic patients were exposed to environmental temperatures of 15, 20 and 24 C. (59, 68 and 75.2 F.). The relative humidity in each case was maintained at 20 per cent. The time of exposure at 24 C. (75.2 F.) was three hours; at 20 C. (68 F.), two and one-half hours, and at 15 C. (59 F.), two hours, the duration being lessened at the lower temperatures because of the discomfort experienced by the subject. Measurements

5. Freeman, H.; Linder, F. E., and Nickerson, R. F.: The Bilateral Symmetry of Skin Temperature, J. Nutrition **13**:39 (Jan.) 1937.

of the skin temperature were made at thirty minute intervals throughout the period of exposure, but in this paper only the initial and final temperatures will be discussed. The initial reading was made immediately on the subject's reclining when the environmental temperature was 24 C. but after thirty minutes when it was 20 or 15 C.

Exposure to these various levels of environmental temperature is characterized by loss of heat from the organism, with a resulting steady fall in skin temperature.[6] This effect becomes, of course, more marked at the lower room temperatures. The decrease in skin temperature is more rapid in the early part of the experimental period and is more evident on the extremities than on the trunk. Despite the general tendency to a fall in surface temperature, there was noted a great deal of individual variation in response, particularly on the hands and feet. At this point it may be mentioned that studies of skin temperature have shown that the extremities are more active in this respect [7] and give a truer indication of the metabolic status [8] of the organism than other portions of the body surface.

Consideration of the initial temperatures at a room temperature of 15 C. (59 F.) (table 1) shows that the trunk and upper portions of the extremities of the patients were slightly warmer, while the normal subjects had slightly higher temperatures over the more distal portions of the extremities. However, there were no striking differences between the two types of subjects.

After two hours of exposure to cold, the normal subjects showed distinctly higher temperatures on the hands and, to a lesser degree, on the feet. In short, despite the fact that the initial levels of temperature of the normal control subjects and the patients were essentially the same, the extremities of the patients cooled to a greater degree. This is seen in the values in the third column of data in table 1. It is also evident that the greater reactive tendency of the patients in response to cold was consistent over various portions of the body surface, for at nine of the ten points measured the decreases were greater in the psychotic group.

At 20 C. (68 F.) the initial temperature level of the extremities was definitely higher for the patients than for the normal subjects (table 1). In the psychotic group the thenar eminence was warmer by 0.8 C. (1.4 F.), the finger by 2.4 C. (4.3 F.) and the foot by 1.4 C. (2.5 F.). On the trunk, however, the skin temperatures of the two groups were similar.

Exposure to this environment for two and one-half hours resulted in the temperature of the extremities remaining at a higher level in the patients and that of the trunk in the normal subjects.

It appeared on the whole that in the schizophrenic subjects a greater change took place on the trunk and lower extremities, while the normal persons exhibited a slightly more marked effect on the upper extremities.

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6. (*a*) Freeman, H., and Nickerson, R. F.: Skin and Body Temperatures of Normal Individuals Under Cold Conditions, J. Nutrition **15**:597, 1938. (*b*) Freeman, H., and Lengyel, B. A.: The Effects of High Humidity on Skin Temperature at Cool and Warm Conditions, ibid. **17**:43, 1939.

7. Hardy, J. D., and Du Bois, E. F.: Basal Metabolism, Radiation, Convection and Vaporization at Temperatures of 22 to 35° C., J. Nutrition **15**:477, 1938.

8. Maddock, W. G., and Coller, F. A.: Skin Temperature of the Extremities and Basal Heat Production, Proc. Soc. Exper. Biol. & Med. **30**:916, 1933.

The results of this study indicate, therefore, that the extremities of the patients were initially warmer, but that in general the degree of cooling was essentially similar to that of the normal subjects.

At 24 C. (75.2 F.) (table 1) the initial temperature readings showed marked differences between the patients and the normal subjects. In nine of the areas the patients showed higher temperatures. In the patients the values for the thumbs were higher by 1.9 C. (3.4 F.), for the fingers by 3.4 C. (6.1 F.) and for the feet by 1.2 C. (2.2 F.). These initial differences between patients and normal subjects are greater than have hitherto been observed in this series of investigations. It

TABLE 1.—*Means of Skin Temperatures of Three Sets of Ten Patients and Ten Normal Controls Obtained at Ten Points on the Skin After Exposure to Three Environmental Temperatures, 15, 20 and 24 C., at a Constant Relative Humidity of 20 per Cent*

Point on Skin	Type of Subject*	Air Temperature, 15 C. (59 F.) Skin Temperature				Air Temperature, 20 C. (68 F.) Skin Temperature				Air Temperature, 24 C. (75.2 F.) Skin Temperature			
		Initial, C.	Final, C.	Change C.	Change F.	Initial, C.	Final, C.	Change C.	Change F.	Initial, C.	Final, C.	Change C.	Change F.
Forehead...	N	30.5	29.7	0.8	1.44	32.2	31.8	0.4	0.72	31.8	31.8	0.0	0.0
	P	30.3	29.4	0.9	1.6	31.4	31.3	0.1	0.18	31.8	31.9	—0.1	—1.8
Chest.....	N	30.5	29.3	1.2	2.2	32.1	31.1	1.0	1.8	31.9	31.3	0.6	1.08
	P	30.8	29.8	1.0	1.8	32.0	31.1	0.9	1.62	32.0	31.2	0.8	1.44
Abdomen...	N	31.6	29.4	2.2	3.96	32.5	31.1	1.4	2.5	32.6	31.4	1.2	2.16
	P	32.0	29.3	2.7	4.86	32.6	30.6	2.0	3.6	32.7	31.2	1.3	2.34
Upper part of arm	N	31.5	29.4	2.1	3.78	32.5	31.0	1.5	2.7	32.4	31.0	1.4	2.52
	P	32.0	29.7	2.3	4.14	32.4	30.6	1.8	3.24	32.8	30.5	2.3	4.14
Lower part of arm	N	31.7	28.9	2.8	5.05	32.6	30.7	1.9	3.42	32.2	29.7	2.5	4.5
	P	32.1	29.2	2.9	5.22	32.6	31.0	1.6	2.88	32.9	29.6	3.3	5.94
Thenar eminence	N	29.0	25.8	3.2	5.76	29.6	27.4	2.2	3.96	28.5	25.5	3.0	5.14
	P	29.0	24.5	4.5	8.1	30.4	28.6	1.8	3.24	30.4	26.2	4.2	7.56
Finger.....	N	23.8	22.1	1.7	3.1	24.4	22.7	1.7	3.06	23.9	22.9	1.0	1.8
	P	23.5	19.9	3.6	6.48	26.8	25.6	1.2	2.16	27.3	23.7	3.6	6.48
Upper part of leg	N	29.8	28.0	1.8	3.24	31.1	29.6	1.5	2.7	31.3	29.9	1.4	2.52
	P	30.0	27.5	2.5	4.5	31.8	29.3	2.5	4.5	31.5	29.6	1.9	3.42
Lower part of leg	N	29.8	26.7	3.1	5.58	30.2	28.2	2.0	3.6	31.3	29.2	2.1	3.74
	P	29.6	26.3	3.3	5.94	30.8	28.1	2.7	4.87	31.4	28.8	2.6	4.68
Foot.....	N	23.3	22.7	5.6	10.08	28.0	23.9	4.1	2.38	28.7	25.2	3.5	6 3
	P	27.9	22.1	5.8	10.44	29.4	24.5	4.9	8.82	29.9	25.5	4.4	7.92

* N indicates normal control subjects; P, patients.

must be remembered that on this occasion the readings were taken immediately after exposure to the laboratory conditions, while in the studies previously described they were obtained after thirty minutes of exposure. In the previous series it is probable that the exposure of thirty minutes allowed some adaptation of the skin temperature, with a resultant diminution of the differences between the two types of subjects.

Exposure to a temperature of 24 C. (75.2 F.) for three hours tended to diminish the differences seen initially between the patients and the normal subjects. The patients were still warmer than the normal controls, but now only over the extremities instead of the entire body surface, as previously. At all points except the forehead the decrease in temperature was greater for the patients. In short, there was greater cooling in the schizophrenic subjects.

Thus far, the data present two points of interest. The extremities of schizophrenic subjects tend initially to be warmer than those of normal subjects and to cool at a more rapid rate. The question arises as to the relationship between the two facts. Is the more intense cooling of the patients a purely physical phenomenon, dependent on their higher initial temperature, or is it the result of dysfunction of a physiologic process? The answer may be obtained from consideration of two sets of data. First, at 15 C. (59 F.) the initial temperatures of schizophrenic and of normal subjects are essentially at the same level. Nevertheless, the fall in temperatures of the psychotic group is the greater. This seems to indicate a slight correlation between the amount of cooling and the initial temperature. In addition, the data obtained at 24 C. (75.2 F.) have been analyzed from this point of view. It was found that the average rate of cooling of the thumb in a thirty minute interval bears no relation to the initial temperature. It is, therefore, largely an independent phenomenon. In addition, this rate of fall in temperature is greater in the patients than in the normal subjects. One may conclude therefore that the more rapid cooling observed in the schizophrenic group is a physiologic characteristic of that group.

The next investigation was carried out under warm conditions. The environmental temperature was 32 C. (89.6 F.), and the relative humidity, 20 per cent. Ten patients and 10 normal subjects were exposed for three hours, measurements of temperature being taken immediately on the subject's reclining and every thirty minutes thereafter.

As the environmental temperature was above the "neutral" zone for skin temperatures, a heating trend was seen.[7] The skin temperature rose more rapidly and to a greater extent on the extremities. The entire body surface tended to become more uniform in temperature, contrary to what is found under cool conditions.

The initial temperatures of the extremities (table 2) were again higher in the patients than in the normal controls, the most marked difference being found on the hands. These differences were not as great as those at 24 C. because even the few minutes of exposure to the high temperature before the readings were made caused a rise in skin temperature and at higher levels of skin temperature differences between individual subjects are lessened.

At the end of the experimental period the patients and normal subjects attained essentially the same levels. The corresponding mean values were more similar than has hitherto been noted.

In reaching this level, however, the temperature of the hands of the normal subjects rose to a greater extent than that of the patients. Thus, for the first time, one sees a greater degree of reactivity in the normal subjects. Since this difference depends primarily on the fact that the normal control subjects were initially cooler, its interpretation is somewhat doubtful. It is difficult to say whether the lesser increase in the schizophrenic patient was due to inability of the blood vessels to dilate or to the fact that the environmental temperature was such as to result in essentially a maximum level for skin temperature.

In the experiments thus far described the behavior of skin temperature was studied under constant environmental conditions. In the present investigation a change in this procedure was made.

The environmental temperature was initially held at 24 C. (75.2 F.), but after the first thirty minutes was increased until in an hour it had reached 44 C. (110.2 F.), at which it was maintained for an hour. The relative humidity was kept at 20 per cent. Twenty normal subjects and 20 schizophrenic patients were exposed to these conditions. Readings were taken immediately on the subject's reclining (at 24 C.) and every thirty minutes thereafter, the last measurements being made after the exposure of the subject to a temperature of 44 C. for one hour.

TABLE 2.—*Means of Skin Temperature of Ten Normal and Ten Schizophrenic Subjects Exposed to an Environmental Temperature of 32 C. and a Relative Humidity of 20 per Cent for Three Hours*

Point on Skin	Type of Subject*	Initial Temperature, C.	Final Temperature, C.	Change in Temperature	
				C.	F.
Forehead	N	33.53	34.93	1.40	2.52
	P	33.20	34.96	1.76	3.17
Chest	N	33.66	34.74	1.08	1.94
	P	33.66	34.82	1.16	2.09
Abdomen	N	34.13	34.72	0.59	1.06
	P	34.09	34.68	0.59	1.06
Upper part of arm	N	33.96	34.72	0.76	1.77
	P	33.98	34.82	0.84	1.51
Lower part of arm	N	33.85	34.68	0.83	1.49
	P	34.07	34.67	0.60	1.08
Thumb	N	31.68	33.48	1.80	1.44
	P	32.65	33.55	0.90	1.62
Finger	N	28.99	32.91	3.92	7.06
	P	30.82	32.77	1.95	5.51
Upper part of leg	N	33.02	34.22	1.20	2.16
	P	33.15	34.23	1.08	1.94
Lower part of leg	N	33.13	33.99	0.86	1.55
	P	33.30	33.92	0.62	1.12
Foot	N	31.14	31.19	0.05	0.09
	P	31.56	31.64	0.08	0.14

* N indicates normal control subjects; P, patients.

The attainment of such high environmental temperatures provides a severe test for the organism. At the initial condition the subject loses heat rapidly, the main channels being through radiation and conduction. At 44 C., however, heat loss is no longer possible. The person under test is absorbing heat and undergoes a rise in body temperature which can be offset only through the medium of evaporation through the skin and lungs. Vasodilatation reaches its maximum level, and stress is placed on the sweating mechanisms. As a result, there is a rapid rise in skin temperature to a level between 36 and 37 C. (96.8 and 98.6 F.), with practically complete uniformity of temperature throughout the body surface. However, in these studies not merely the temperatures of individual subjects were uniform. The temperatures of all persons on

all areas were found to vary within a very narrow range. In short, both the individual and the group became homogeneous.

In table 3 is seen the same initial tendency (at 24 C.) to warmer extremities on the part of the patients. The final temperatures, however, exhibited the similarity which was found at 32 C. Patients and normal subjects were remarkably alike. The final column, containing the total rises in temperature, again indicates that the change was greater in the normal subjects.

It is evident, then, that patients are fully as capable of vasodilatation as normal subjects and that the response in skin temperature to external heat may be essentially normal in the schizophrenic subject.

TABLE 3.—*Means of Skin Temperatures in Twenty Normal and Twenty Schizophrenic Subjects Exposed for Three Hours to Environmental Temperatures Rising from 24 to 44 C. with Relative Humidity of 20 per Cent*

Point on Skin	Type of Subject*	Initial Temperature, C.	Final Temperature, C.	Change in Temperature	
				C.	F.
Forehead	N	31.44	36.98	5.54	9.97
	P	31.28	36.75	5.47	9.84
Chest	N	31.52	37.12	5.60	10.08
	P	31.57	37.00	5.43	9.77
Abdomen	N	32.12	36.59	4.47	8.04
	P	32.01	36.69	4.68	8.24
Upper part of arm	N	31.92	37.02	5.10	9.18
	P	32.14	37.02	4.88	8.78
Lower part of arm	N	31.83	36.84	5.01	9.02
	P	32.12	36.76	4.64	8.35
Thumb	N	29.55	37.00	7.45	13.41
	P	30.43	36.99	6.56	11.80
Finger	N	26.69	36.95	10.26	18.47
	P	27.86	37.04	9.18	16.52
Upper part of leg	N	31.00	36.51	5.51	9.92
	P	31.18	36.56	5.38	9.68
Lower part of leg	N	30.91	35.96	5.05	9.09
	P	31.03	36.07	5.04	9.07
Foot	N	29.18	36.73	7.55	13.59
	P	29.58	36.67	7.09	12.76

* N indicates normal control subjects; P, patients.

In the previous studies the reactions of skin temperature were measured under conditions of low humidity, when the factor of evaporation was essentially unchecked. Since schizophrenic patients are commonly considered to have clammy extremities, it occurred to me to test the efficacy of the sweating mechanisms by exposing the subjects to high humidities, both at low and at high temperatures.

Ten matched pairs of patients and subjects reclined in the laboratory for three hours while the relative humidity was raised from an initial level of 20 to a final level of 90 per cent. This was done on two separate days at environmental temperatures of 24 and 32 C. (75.2 and 89.6 F.), respectively. As the subjects had already been studied at the same environmental temperatures with a constant low humidity of 20 per cent, the latter values served as a base line to determine the

effect of the increased humidity. Higher values for skin temperature were obtained for corresponding periods on the humid days, and the net effect of increasing the humidity was obtained by subtracting the final reading on the dry (20 per cent) day from that obtained on the humid (90 per cent) day. Since the two experimental days were only twenty-four hours apart and since the initial environmental conditions were the same, the initial skin temperatures were similar, so that the final value may be taken as approximately correct.

The effect of increasing the humidity of the atmosphere resulted in a rise in skin temperature which was slight on the forehead and trunk but marked on the extremities (table 4). The resulting increase in temperature was similar at

TABLE 4.—*Means of Differences in Skin Temperatures of Ten Normal and Ten Schizophrenic Subjects Obtained at Relative Humidities of 20 and 90 per Cent at Two Environmental Temperatures of 24 and 32 C.*

Point on Skin	Type of Subject*	Means of Differences at 24 C. (75.2 F.) and Relative Humidity of 90 - 20% Change in Temperature		Means of Differences at 32 C. (89.6 F.) and Relative Humidity of 90 - 20% Change in Temperature	
		C.	F.	C.	F.
Forehead	N	0.50	0.90	0.20	0.36
	P	0.27	0.49	0.24	0.43
Chest	N	0.36	0.63	0.13	0.23
	P	0.24	0.43	0.06	0.11
Abdomen	N	0.30	0.54	0.11	0.20
	P	0.22	0.39	0.00	0.00
Upper part of arm	N	0.54	0.97	0.20	0.36
	P	0.73	1.31	0.14	0.25
Lower part of arm	N	0.90	1.62	0.40	0.72
	P	0.83	1.47	0.43	0.77
Thumb	N	2.21	3.98	1.84	3.31
	P	0.56	1.01	1.71	3.08
Finger	N	3.29	5.92	2.57	4.63
	P	3.03	5.45	2.59	4.66
Upper part of leg	N	0.59	1.06	0.49	0.88
	P	0.48	0.87	0.25	0.45
Lower part of leg	N	0.93	1.67	0.44	0.79
	P	0.50	0.90	0.15	0.27
Foot	N	1.99	3.56	3.42	6.56
	P	1.74	3.13	2.93	5.27

* N indicates normal controls; P, patients.

the two environmental temperatures, somewhat to my surprise, since a greater effect was expected at 32 than at 24 C. An attempt to explain this phenomenon has been offered in another publication.[6b]

The results show that high humidity has a warming effect on the skin. This is evidently due to inhibition of heat loss resulting from evaporation from the skin. It had been considered that of two subjects with very different amounts of moisture on the skin, the person who had the more moist skin would be affected less by a rise in humidity than the person with a dry skin, for the vapor tension of the atmosphere surrounding his skin was already relatively saturated.

Consideration of the data shows no essential differences between patients and normal subjects at either 24 or 32 C. The rise in tempera-

ture shown by the patients was slightly less than that shown by the normal controls, but not sufficiently so to be considered of any importance. The conclusion must be reached, therefore, that patients and normal subjects do not differ in this respect at these environmental temperatures.

At all the environmental temperatures in previous experiments, rectal temperatures were taken directly after the skin temperatures were measured. The results are shown in table 5. At all temperatures except 44 C. (110.2 F.) there was a fall in rectal temperature, due to loss of heat and to relaxation. Only when the environmental temperature rose to high levels was this trend checked and overcome, and even under these conditions the high temperature had to be maintained for hours before an appreciable rise in rectal temperature was noted. There is a

TABLE 5.—*Means of Rectal Temperatures of Normal and Schizophrenic Subjects Exposed to Varying Environmental Conditions*

Air Temperature, C.	Type of Subject*	Initial Temperature, C.	Final Temperature, C.	Change in Temperature	
				C.	F.
15	N	36.81	36.65	0.16	0.29
	P	36.82	36.59	0.23	0.41
20	N	36.78	36.21	0.57	1.03
	P	36.67	36.20	0.47	0.85
24	N	37.21	36.61	0.60	1.08
	P	37.09	36.54	0.55	0.99
32	N	37.02	36.87	0.15	0.27
	P	37.11	37.04	0.07	0.13
24-44	N	36.96	37.21	0.25	0.45
	P	37.08	37.29	0.21	0.38

* N indicates normal controls; P, patients.

marked lag, then, between the skin and the rectal temperature, and it is unwise to predict the action of one in terms of the other at any given time.

The initial levels of rectal temperature were similar in normal and schizophrenic subjects. The reactions to both cold and hot conditions were also the same in the two groups. I am led to the conclusion, therefore, that in this respect schizophrenic patients act like normal persons.

COMMENT

Before any conditioning process has begun or has had much effect, the temperature of the extremities of schizophrenic patients is not lower than that of normal subjects. These patients initially tend to have warmer hands and feet than nonpsychotic persons. The greater supply of heat is dependent on the fact that either the amount of blood to that area per unit of time is increased or that the production of heat by the tissue cells is augmented or both. In the case of schizophrenic subjects the evidence

from previous research is that neither the amount of blood to the tissues [9] nor the heat production is greater than normal; in fact, quite the contrary. Certainly, it cannot be assumed that more heat is transmitted to the tissues via the blood stream, since the low blood pressure [10] and the slow rate of blood flow [11] tend to preclude this possibility. The second hypothesis is contradicted by the normal level of the rectal temperatures (table 5) and the somewhat lowered rate of oxygen consumption found in this psychosis.[1] The possibility occurs, then, that the increased warmth of the skin may be due to vasodilatation dependent on loss of vasoconstrictor tone. In view of the fact that chronic vasodilatation occurs in decorticate [12] and anhypothalamic [13] preparations, as well as with lesions involving the autonomic nervous system per se, it seems presumptuous, in the present state of knowledge, to attempt to localize the source of this type of abnormality.

Under cold conditions it has been seen that schizophrenic subjects tend to exhibit greater cooling of the extremities than normal persons. Abnormally rapid decreases in body temperature on exposure to cold have been found in a variety of experimental conditions in animals, e. g., after adrenalectomy, sympathectomy and hypophysectomy. Since the present data on rectal temperatures do not show any differences between patients and normal subjects, one cannot attribute this phenomenon specifically to any of the aforementioned causes. On the other hand, rectal temperatures are slow to change, and it is possible that the periods of exposure were not sufficiently long or severe to demonstrate any abnormality. A further possibility may lie in the sensitization of sympathectomized organs to sympathetic stimuli.[14] Freeman, Smithwick and White [15] found a marked fall of skin temperature in a sympathectomized

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9. Looney, J. M., and Freeman, H.: Volume of Blood in Normal Subjects and in Patients with Schizophrenia, Arch. Neurol. & Psychiat. **34**:956 (Nov.) 1935.

10. Freeman, H.; Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia, Arch. Neurol. & Psychiat. **27**:333 (Feb.) 1932.

11. Freeman, H.: Variability of Circulation Time in Normal and Schizophrenic Subjects, Arch. Neurol. & Psychiat. **39**:488 (March) 1938.

12. Pinkston, J. O.; Bard, P., and Rioch, D. M.: Responses to Changes in Environmental Temperature After Removal of Portions of the Forebrain, Am. J. Physiol. **109**:515 (Sept.) 1934.

13. Keller, A. D., and Hare, W. K.: Hypothalamus and Heat Regulation, Proc. Soc. Exper. Biol. & Med. **29**:1069, 1932.

14. Elliott, T. R.: The Action of Adrenalin, J. Physiol. **32**:401, 1905.

15. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy to Adrenalin, and to Adrenal Secretion Resulting from Insulin Hypoglycemia, Am. J. Physiol. **107**:529, 1934. Smithwick, R. H.; Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity, Arch. Surg. **29**:759 (Nov.) 1934.

extremity after administration of ephinephrine or exposure to cold. It is possible that the greater cooling of the extremities of the patients on exposure to cold may be of a similar nature. If this is true, it supports the hypothesis previously advanced of lessened reactivity of the sympathetic nervous system.

The data on the hot days show that the skin temperature of the schizophrenic patient reacts in a fashion comparable to that of the normal subject. He is capable of as great vasodilatation. The implication, therefore, is that the parasympathetic mechanisms function at a normal level of activity.

The results of the humid days are confirmatory in this respect. As a mechanism inhibiting heat loss at these levels of environmental temperature, high humidity tends to maintain the caliber of the cutaneous vessels and therefore acts in the capacity of a heat stimulus.

SUMMARY

Schizophrenic and normal subjects were exposed to varying environmental conditions, in the nude and under fasting conditions. Skin and rectal temperatures were measured by means of thermocouples. It was found that immediately after exposure the schizophrenic patients tended to have warmer extremities than the normal subjects. Exposure to cold conditions (15, 20 and 24 C. [59, 68 and 75.2 F.]) resulted consistently in greater cooling of the skin in the patients than in the normal controls. Exposure to hot conditions (44 C. [110.2 F.]) resulted in no difference in the response of normal and of schizophrenic subjects. Exposure to high humidity at low and high temperatures showed no difference between the patients and the normal subjects. The rectal temperatures of schizophrenic and normal subjects reacted similarly under all conditions.

CONCLUSIONS

The greater reactivity of schizophrenic subjects to cold conditions implies a dysfunction of the neural mechanisms controlling vasoconstrictor tone. Vasodilatation in schizophrenic subjects may be normal.

Case Reports

THE CENTRAL VISUAL SYSTEM

Evidence Against Bilateral Representation Through the Splenium of the Corpus Callosum

OLAN R. HYNDMAN, M.D., IOWA CITY

It has been consistently demonstrated that unilateral occipital lobectomies in man result in homonymous hemianopia with sparing of central vision.[1] This has also been my experience in 5 cases of occipital lobectomy. It has also been adequately demonstrated that lesions which destroy the posterior aspect of the temporal lobe down to the temporal horn produce complete homonymous hemianopia.[1b]

The explanation of these findings with reference to the mechanism of central vision is controversial. In short, two schools have evolved. One proposes that macular vision is bilaterally represented.[2] The geniculostriate fibers subserving macular vision not only lead to the visual cortex of the same side but send collaterals through the splenium of the corpus callosum to the opposite visual cortex. The latter fibers are far enough anterior to escape injury by an occipital lobectomy, provided the coronal plane of excision is not carried farther forward than the posterior tip of the corpus callosum. Among those who have endorsed this explanation are Lenz,[3] Pfeifer,[4] Foerster[5] and Penfield and his associates.[1b]

From the department of surgery, neurosurgical service, the State University of Iowa College of Medicine.

1. (*a*) Horrax, G., and Putnam, T. J.: Distortions of the Visual Fields in Cases of Brain Tumor, Brain **55**:499-523, 1932. (*b*) Penfield, W.; Evans, J. P., and MacMillan, J. A.: Visual Pathways in Man, with Particular Reference to Macular Representation, Arch. Neurol. & Psychiat. **33**:816-834 (April) 1935.

(This paper[1b] and that of Putnam[6] furnish a more complete bibliography relevant to this subject than will be given here.)

2. Putnam, in discussing a paper by Penfield, Evans and MacMillan,[1b] pointed out that Wilbrand was the first to suggest bilateral representation of macular fibers (Fulton,[11] p. 358). He expressed the opinion that bifurcation of the fibers occurred at the chiasm. This concept receives no support, since it is known that a complete lesion of the optic tract anterior to the primary optic nucleus produces complete hemianopia.

3. Lenz, G.: Zur Pathologie der cerebralen Sehbahn unter besonderer Berücksichtigung ihrer Ergebnisse für die Anatomie und Physiologie, Arch. f. Ophth. **72**:1 and 197, 1909.

4. Pfeifer, R. A.: Myelogenetisch-anatomische Untersuchungen über den zentralen Abschnitt der Sehleitung, in Foerster, O., and Wilmanns, K.: Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, Berlin, Julius Springer, 1925, no. 43.

5. Foerster, O.: Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre, J. f. Psychol. u. Neurol. **39**:463-485, 1929.

Opposition to the preceding theory was taken by Putnam,[6] after having failed to demonstrate visual fibers in the corpus callosum by anatomic and histologic studies. Putnam referred to the works of van Valkenburg [7] and Beevor [8] as supporting his observations.

The evidence which has been taken to support a possible bilateral representation of macular vision is based on the following observations:

1. Histologic studies have indicated that the primary cortical representation of macular vision is entirely within the occipital pole. For example, Putnam [9] stated that the macula appeared to be represented in a wedge-shaped area, with its apex directed anteriorly, in the striate cortex. This area extended not less than 2, and not more than 3, cm. anterior to the occipital pole in the specimen studied. Nevertheless, when the occipital lobe is amputated even farther anterior than this macular vision is spared.

2. Holmes and Lister [10] reported a case of complete loss of central vision with sparing of peripheral vision due to a gunshot wound which had injured the tip of each occipital lobe. The extent of the lesion was determined by surgical inspection, but Fulton [11] stated that since nothing corresponding to this has been found after occipital lobectomy in man, one is forced to the conclusion either that Holmes and Lister's unverified lesion was larger than they suspected or that in taking visual fields during the World War period a relative scotoma was mistaken for a complete defect. Present day perimetric refinements were not available at that time.

3. Foerster [5] reported the case of a patient in whom a tumor of the corpora quadrigemina was suspected. At operation the corpus callosum was incised 2 cm. from the posterior end, and the right occipital lobe was resected about 5 cm. from the tip. Before operation the visual fields were normal, but afterward they revealed complete left homonymous hemianopia passing through the fixation point. Foerster attributed the split macula to the incision of the splenium.

No case has been reported in which from a clinical standpoint incontrovertible evidence has been furnished for or against a possible role of the corpus callosum in central vision. I believe that the case reported here furnishes that evidence.

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6. Putnam, T. J.: Studies on the Central Visual Connections: III. The General Relationship Between the External Geniculate Body, Optic Radiation and Visual Cortex in Man; Report of Two Cases, Arch. Neurol. & Psychiat. **16**: 566-596 (Nov.) 1926.

7. van Valkenburg, C.: Experimental and Pathologico-Anatomical Researches on the Corpus Callosum, Brain **36**:119-165, 1913.

8. Beevor, C. E.: On the Course of the Fibers of the Cingulum and the Posterior Parts of the Corpus Callosum and Fornix in the Marmoset Monkey, Phil. Tr. Roy. Soc., London **182**:135-199, 1891.

9. Putnam, T. J.: Studies on the Central Visual System: IV. The Details of the Organization of the Geniculostriate System in Man, Arch. Neurol. & Psychiat. **16**:683-707 (Dec.) 1926.

10. Holmes, G., and Lister, W. T.: Disturbances of Vision from Cerebral Lesions, with Special Reference to the Cortical Representation of the Macula, Brain **39**:34-73, 1916.

11. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

REPORT OF A CASE

F. T., a white man aged 43, who was referred by Dr. F. A. Ely, of Des Moines, Iowa, on Dec. 27, 1938, had become ill two months before with severe frontal headache, nausea and vomiting. At this time he also began to experience transient attacks of numbness and weakness in the right arm, hand and foot. These attacks lasted about thirty seconds and occurred from one to five times daily. He had experienced two attacks of unconsciousness, lasting about one

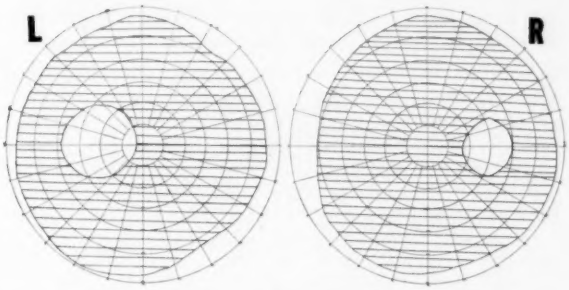

Fig. 1.—Visual fields before operation. The hatched area represents the field of vision.

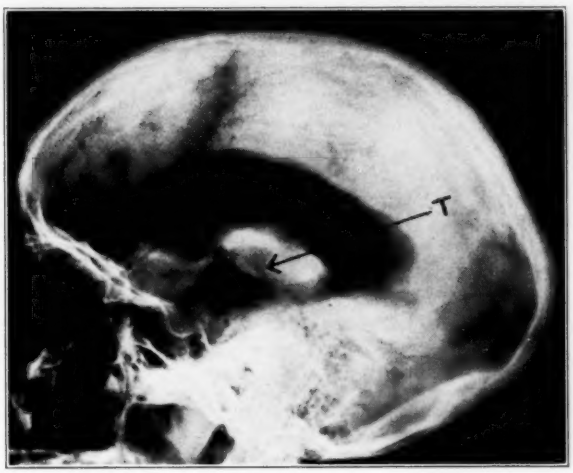

Fig. 2.—Ventriculogram, lateral view. *T* indicates a filling defect in the posterior aspect of the third ventricle, which outlines the anterior border of the tumor.

minute. They were preceded by a visual disturbance such that objects appeared wavy, as if seen through heat waves.

Examination.—General physical examination gave essentially normal results.

Neurologic examination gave essentially normal results except for the following: The right pupil was 6 and the left 7 mm. in diameter; the pupils were

regular and reacted well to light and in accommodation; the choking of the optic disks was 3 plus D.

Laboratory Studies.—Urinalysis and examination of the blood, including the Wassermann test, gave normal results. Spinal puncture was not done.

Special Examinations.—Visual Fields and Visual Acuity:[12] In spite of the choking of the disks, the visual fields on Dec. 28, 1938, were full (fig. 1). (The visual fields recorded in this report were taken with the Bjerrum screen; the screen was 1,200 mm. from the eye; a 1 mm. target was used; the patient's eyes were carefully watched for movements that might occur during the tests.) Visual

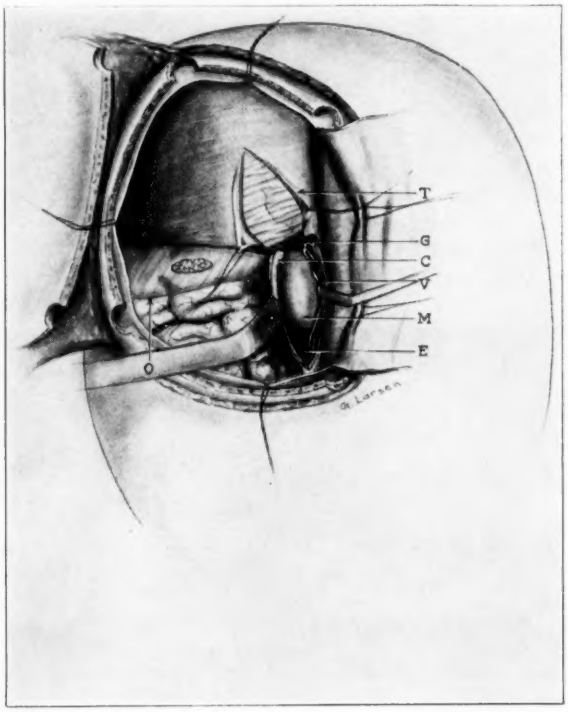

Fig. 3.—Drawing to illustrate the operative procedure and appearance of the tumor. The occipital lobe was resected at the first operation, and the corpus callosum was sectioned at the second operation.

O indicates plane of exsection of the right occipital lobe. The plane passes through the common junction of the ventricular horns, exposing the glomus of the choroid plexus. *T* designates reflection of the cerebellar tentorium after cutting the incisura; *G*, the vein of Galen; *C*, the cut surface of the corpus callosum; *V*, the two veins of the tela choroidea; *M*, the tumor, and *E*, the third ventricle, exposed at the anterior border of the tumor.

12. Miss Esther Schlue made the visual field studies on this patient, and Dr. Henry D. Keislar, of the department of ophthalmology, made the determinations of visual acuity.

acuity in the right eye was 6/6 —2, and 6/6 with a + 0.50 sph., and in the left eye, 6/21, and 6/9 with a + 0.50 sph. ⌒ + 0.50 cyl., ax. 145.[13]

Ventriculographic Examination: A ventriculogram revealed symmetric dilatation of the lateral ventricles without shift or filling defect. The lateral view showed an unmistakable filling defect in the posterior aspect of the third ventricle (fig. 2).

First Operation.—On the diagnosis of a tumor of the pineal body or a tumor in the posterior aspect of the third ventricle, an occipitoparietal flap was turned down on the right side. The exposure was intended to be between the hemispheres and through the corpus callosum. In spite of release of air and fluid from the ventricles, the brain became so swollen that it would have been unwise to proceed. Because the brain was too swollen to replace the bone flap, I resected the right occipital lobe to provide room and make possible an easy exposure at a later date. The occipital lobe was resected in a coronal plane that seemed exactly tangent to the posterior tip of the corpus callosum (fig. 3). The posterior horn was opened thereby and the glomus of the choroid plexus exposed.

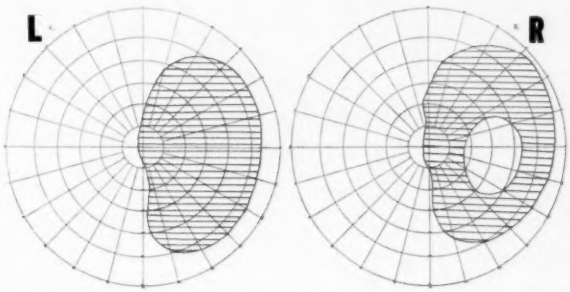

Fig. 4.—Visual fields taken ten days after occipital lobectomy, showing sparing of macular vision.

Second Test of Visual Fields and Visual Acuity.—The patient made an uneventful recovery, and on Jan. 9, 1939, ten days after the operation, the visual fields revealed left homonymous hemianopia with sparing of macular vision[14] (fig. 4).

Visual acuity in the right eye was 6/12 and 6/30 in the left.

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13. Visual acuity of 6/6 —2 indicates that the patient reads letters at 6 feet (182 cm.) which should normally be read at that distance except that he misses two letters of the group. The reading "6/9 with a + 0.50 sph. ⌒ + 0.50 cyl., ax. 145" indicates that he read at 6 feet letters which should normally be read at 9 feet (274 cm.). The correction used is a convex sphere of 0.50 D. plus a convex cylinder of 0.50 D., the axis of which is 145 degrees.

14. The problem concerning macular vision and its representation on the field chart is not a simple one. For this reason, I am recording the charts exactly as they were determined on the Bjerrum screen, without modification. Although the patient's eyes were carefully watched for slight movements, it is not unlikely that a patient with split macular vision will shift his vision slightly toward the blind side in order to see the fixation point. Dr. C. S. O'Brien, of the department of ophthalmology, believes that visual acuity is a more dependable test of macular vision than determination of the visual fields.

Second Operation.—On January 10 I reopened the wound, with the use of local anesthesia, and, after separating the hemispheres, completely incised the corpus callosum to a point 2¼ inches (5.7 cm.) from its posterior tip (fig. 3). This was measured by means of a strip of cotton the length of which was later determined. The corpus callosum was of normal thickness and was not compressed upward, as is often the case when a pinealoma is present. The vein of Galen was also free and in a normal position. When the tela choroidea was torn, a mass bulging into the third ventricle was disclosed. It had the appearance of normal brain tissue, but a small biopsy specimen showed it to be of gliomatous

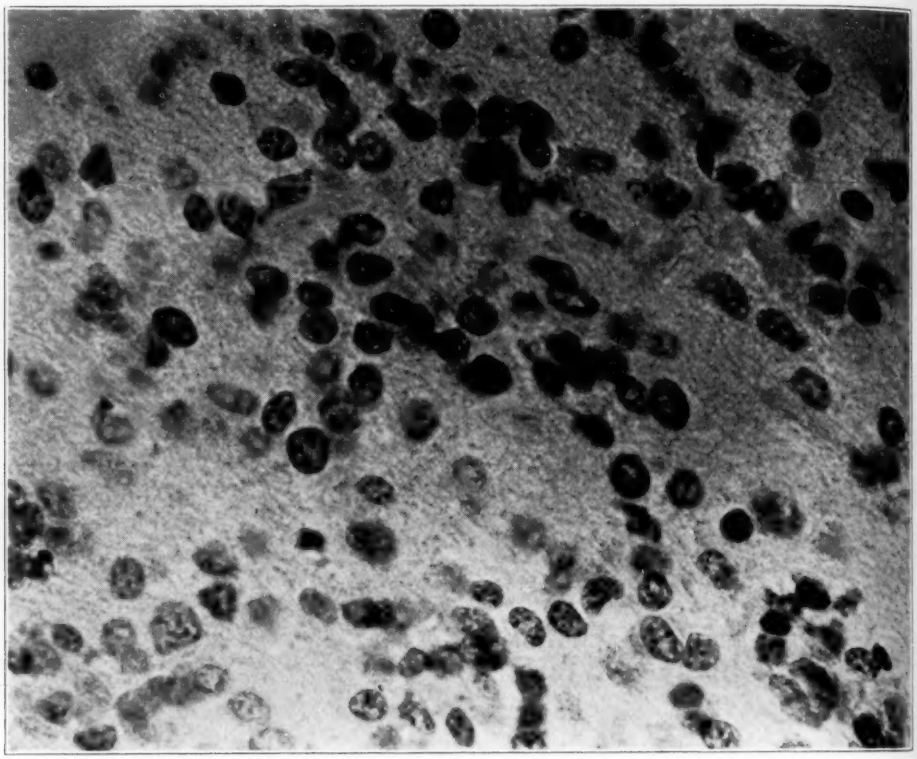

Fig. 5.—Photomicrograph showing cellular structure of the tumor and an occasional mitotic figure; hematoxylin and eosin stain.

structure (fig. 5). I was able to visualize the third ventricle anterior to the mass. Having satisfied myself that the tumor was infiltrating and not removable, I cut the tentorium, as shown in the figure, hoping by such a decompression to restore some circulation of fluid through the aqueduct of Sylvius.

It is interesting that the patient complained of no pain until the incisura was cut. This and light tugging on the straight sinus caused him to experience severe generalized headache, which he could not localize more accurately.

Third Test of Visual Fields.—The patient made such an uneventful recovery that the visual fields were taken on the third postoperative day (fig. 6). Atten-

tion was given only to the central field at this time, and though, for some reason, the line passed even to the right of the fixation point, I believed that the test would demonstrate complete hemianopia.

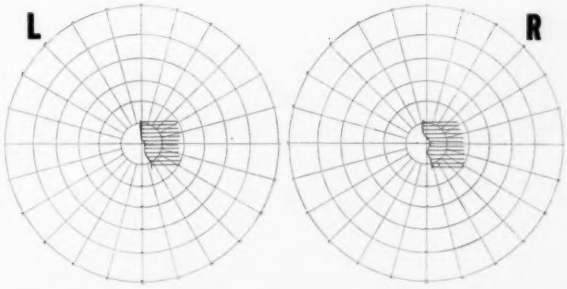

Fig. 6.—Fields taken on the third day after section of the corpus callosum. Attention was given only to the central field. Not only was the hemianopia complete at this time but the line of vision passed to the right of the fixation point (see "Comment").

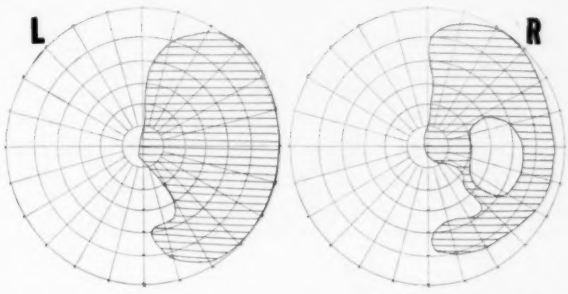

Fig. 7.—Fields taken ten days after section of the corpus callosum, showing return of macular vision.

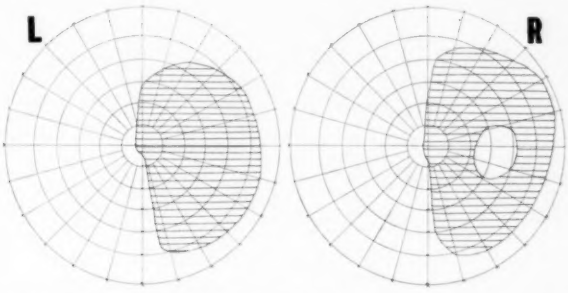

Fig. 8.—Fields taken one month after section of the corpus callosum, showing left homonymous hemianopia with sparing of macular vision.

Fourth Test of Visual Fields and Visual Acuity.—Ten days after the operation the visual fields showed macular sparing (fig. 7). Visual acuity was 6/12 in the right eye and 6/12 in the left.

Course.—The patient continued to improve, and roentgen therapy was instituted. Thirteen days after the second operation the intracranial pressure, as determined by lumbar puncture, was 145 mm. of water when the patient was in the prone position.

Fifth Test of Visual Fields and Visual Acuity.—One month after the second operation the visual fields indicated macular sparing and general improvement in vision, particularly in diminution of the size of the blindspot in the right eye (fig. 8). Visual acuity in the right eye was 6/9, and 6/6 with a + 0.50 sph., and in the left, 6/12 and 6/9 + 3 with a + 0.75 sph. ⌒ + 0.50 cyl., ax. 150.

COMMENT

The visual fields last taken, indicating macular sparing and excellent visual acuity, showed that the patient's central vision was intact. Hence, as determined in this case, the posterior 2¼ inches of the corpus callosum plays no role in a possible bilateral representation of central vision. This result also strongly discredits bilateral representation. An alternative explanation is that cortex representing central vision exists anterior to the plane of section of the occipital lobe in this case.[15] It is interesting in this connection that in Penfield's [1b] fifth case split macular vision was demonstrated. In this patient the occipital lobe was sectioned farther anteriorly than in his other patients, who retained full macular vision. The explanation given by Penfield is that the geniculostriate bundle destined for the corpus callosum had been sectioned.

I believe that the visual fields taken in my case on the third day after section of the corpus callosum are highly instructive. They demonstrated loss of macular vision on the left.[16] Seven days later this portion of the visual field was again intact, and remained so. It is possible that retraction of the mesial cortex just anterior to the plane of section of the occipital lobe resulted in temporary loss of function. While incising the corpus callosum it is necessary to maintain retraction of the cortex in this region with a spatula for some time. This may be the explanation of the split macula in Foerster's [5] case.

CONCLUSIONS

Full macular vision was retained after resecting the right occipital lobe to the tip of the splenium of the corpus callosum, in addition to section of the corpus callosum to a point 2¼ inches (5.7 cm.) from the posterior tip. Consequently, the splenium of the corpus callosum plays no role in retention of central vision.

Central vision is probably, at least in part, represented anterior to the accepted visual cortex and is probably not represented bilaterally.

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15. German and Fox (Observations Following Unilateral Lobectomies, A. Research Nerv. & Ment. Dis., Proc. **13**:378-434, 1934) concluded that in man, though macular representation is predominantly in the occipital pole, some macular fibers are distributed more anteriorly.

16. In fact, macular vision appears to have been impaired bilaterally. It should be borne in mind that the mesial cortices of both hemispheres above the splenium were retracted with spatulas during the operation. It is not far fetched to assume that this accounted for a transient scotoma in the complete macular field.

Abstracts from Current Literature

Anatomy and Embryology

THE EXACT ORIGIN OF THE CORTICO-SPINAL TRACT IN THE MONKEY. PAUL M. LEVIN and F. KEITH BRADFORD, J. Comp. Neurol. **68**:411 (June) 1938.

The origin of the corticospinal tract was studied in 6 macaque monkeys by retrograde cell degeneration of the Nissl substance after interruption of the tract at the fourth cervical level. The monkeys were allowed to survive for varying intervals. Eighty-five per cent of the corticospinal fibers were observed to cross at the pyramidal decussation. There were approximately 2,500 ipsilateral fibers from area 4 of the frontal lobe and 1,000 ipsilateral fibers from areas 1, 2, 3 and 5 of the parietal lobe. Levin and Bradford suggest that the term "Betz cell" be used to include all cortical cells which send axons to the spinal cord, regardless of the size of the cell.

ADDISON, Philadelphia

FURTHER DETERMINATIONS OF THE NUMBERS OF FIBERS AND CELLS IN THE DORSAL ROOTS AND GANGLIA OF THE CAT. DONALD DUNCAN and LESTER L. KEYSER, J. Comp. Neurol. **68**:479 (June) 1938.

Duncan and Keyser repeated their work on the numbers of fibers and cells in the dorsal roots and ganglia of cats. The ganglia to be studied were fixed in a solution of formaldehyde and glacial acetic acid, and the nerves were prepared by the pyridine silver method. The number of cells in a ganglion was determined by counting the nucleoli in every fourth section. Counts were made on 45 ganglia. The total number of fibers was determined in 33 roots. The results obtained from the cervical, thoracic, lumbar and sacral regions are interpreted by Duncan and Keyser as uniformly in favor of equality in numbers of the spinal ganglion cells and the dorsal root fibers.

FRASER, Philadelphia.

THE STRUCTURAL ORGANIZATION OF THE CELIAC GANGLIA. ALBERT KUNTZ, J. Comp. Neurol. **69**:1 (Aug.) 1938.

This report is based on the study of human celiac ganglia and the celiac ganglia of normal and experimental cats. Three series of operations were carried out on the experimental animals: (1) The splanchnic nerves were divided and the upper lumbar segments of the sympathetic trunks extirpated bilaterally; (2) the vagus nerves were divided below the diaphragm, in addition to the preceding operation; (3) nerves extending from the celiac plexus to the stomach and intestine were divided. The animals in the first two series were killed after from twelve to fifteen days, those of the third series earlier. All material was prepared by a modification of Cajal's technic.

The first series of operations showed that a large number, though not all, of the axons which terminate in the celiac ganglia undergo degeneration. Fibers remaining intact were mainly vagus nerve fibers and postganglionic fibers arising in cells of the celiac ganglia. The second set of operations exhibited a larger percentage of degenerating fibers in the bundles which course through the ganglia than did the preparations of ganglia in the first series. The fibers which remained intact represented mainly postganglionic axons which had become incorporated in bundles. In the third series of operations some of the fibers in the proximal portion of the nerves degenerated. Kuntz interprets these as fibers which arise in the enteric plexuses and go to the celiac ganglia.

ADDISON, Philadelphia.

DEVELOPMENT OF THE BRAIN OF AMBLYSTOMA PUNCTATUM FROM EARLY SWIMMING TO FEEDING STAGES. C. JUDSON HERRICK, J. Comp. Neurol. **69**:13 (Aug.) 1938.

This study of the development of the brain of Amblystoma is carried on in stages succeeding those described previously by Coghill and Herrick. About 100 specimens of this species were available for study. The movements of the animals were classified, successively, as strong swimming, late swimming and early feeding and covered a period of development of over two weeks. In the strong swimmers the medial and lateral basal forebrain bundles were clearly defined in the telencephalon, and the lateral bundle extended spinalward to the level of the isthmic sulcus. The spinal and bulbar lemniscus systems were well formed in the medulla oblongata. A succeeding group of strong swimmers, one to four days later, or three to seven days after early swimming, showed a thickened corpus striatum and a dense striatal neuropil. The anterior commissure then contained massive decussations of the medial and lateral forebrain bundles. The fibers of the mesencephalic root of the trigeminus nerve were arranged as in the adult. Late swimmers showed an advance in the myelination of nerve fibers. Myelin appeared in the two motor roots of the trigeminal nerve and in the first motor root of the facial nerve. A few myelinated fibers were present in the motor roots of the ninth and tenth cranial nerves as well as in the fasciculus longitudinalis medialis. In the early feeders myelination was little advanced over the previous stage, except in the spinal cord.

FRASER, Philadelphia.

THALAMUS OF A DOG WITHOUT A HEMISPHERE DUE TO A UNILATERAL CONGENITAL HYDROCEPHALUS. JAMES W. PAPEZ and R. WAYNE RUNDLES, J. Comp. Neurol. **69**:89 (Aug.) 1938.

The brain under investigation was that of a German shepherd dog, 7½ months old. The left cerebral hemisphere was represented by a thin nonnervous shell, which was filled with fluid. On the left side the thalamus, corpus striatum and cerebral peduncles were rudimentary. The internal capsule was very small because of the deficiency of the thalamocortical radiations and of the cortical efferent fibers. In the dorsal thalamus the neothalamic nuclei, namely, the geniculate bodies and the ventral lateral nucleus, were represented by rudiments. The ventral posterior, interventral and center median nuclei were present. The medial nucleus was well preserved, but the nucleus lateralis and the pulvinar were totally absent. The hypothalamus was well developed. The pars ventralis thalami and its contributions to the ventral supraoptic decussations appeared normal. The subthalamic nucleus, substantia nigra reticulata, red nuclei and their fiber connections were present on both sides.

FRASER, Philadelphia.

THALAMIC CONNECTIONS IN A HEMIDECORTICATE DOG. JAMES W. PAPEZ, J. Comp. Neurol. **69**:103 (Aug.) 1938.

For this study the left cerebral hemisphere was almost entirely removed from a dog and the animal killed six months later. In this experiment secondary degeneration of the internal capsule and of the neothalamic nuclei occurred. Papez has been able to divide the thalamic mass into four groups on the basis of their connections (1) with the olfactory centers, (2) with the hypothalamus, (3) with the corpus striatum and (4) with the neocortex.

FRASER, Philadelphia.

THE THALAMIC NUCLEI OF SUS SCROFA. OTHMAR SOLNITZKY, J. Comp. Neurol. **69**:121 (Aug.) 1938.

Four brains of Sus scrofa were used in this study. Each was stained by a different method. The best developed nuclear groups were the anterior, medial and ventral nuclei of the thalamus; this places the pig in a position intermediate

between carnivores and primates. Both the anterior and the midline groups are close to those of the carnivores, but the medial group is similar to that of the primates. The ventral group resembles most closely that of primates. The habenular nuclei are better developed than those in carnivores and primates.

FRASER, Philadelphia.

NOTES ON THE RETINAE OF TWO OPOSSUM GENERA. G. L. WALLS, J. Morphol. **64**:67 (Jan.) 1939.

Sagittal sections of Kolmer-fixed eyes of the common opossum, Didelphis virginiana Kerr, and of the pouchless Central American "mouse opossum," Marmosa mexicana, were studied. Both animals are strongly nocturnal. Their retinas are sauropsidan in type, and their eyes are markedly adapted for scotopic vision. In Didelphis the superior half of the fundus is occupied by a tapetum lucidum of the retinal type, its cells being packed with reflective particles of unknown composition. Such a tapetum is unique among mammals, being "nonocclusible" (*abblendbar*), since migratory fuscin granules and guanin are absent. The retinal capillaries in Didelphis extend to the external limiting membrane, a condition which is known in only four other mammals and possibly is an adaptation to the low permeability of the dense tapetum. Both genera have visual cells of three types—abundant rods and scanty single and double cones. The oil droplets, in the single and double cones which have them, are colorless, and only one is present in the double cones. The members of the double cone are never alike in size or form.

WYMAN, Boston.

THE DEVELOPMENT OF THE CHICK PITUITARY WITH SPECIAL REFERENCE TO THE CELLULAR DIFFERENTIATION OF THE PARS BUCCALIS. HERMANN RAHN, J. Morphol. **64**:483 (May) 1939.

The pars anterior of the hypophysis of the chick is bilobed from about the sixth day of development. The caudal lobe lies nearest the infundibular process, while the cephalic lobe is anterior and gives rise to the pars tuberalis. The caudal lobe contains typical basophilic, acidophilic and chromophobic cells, but the acidophils of the cephalic lobe stain weakly and are otherwise different from those of the caudal lobe. The hypophysial stalk begins to retrogress on the ninth day, but the pars tuberalis continues to grow, reaching the floor of the brain at about the 11 day stage, enclosing the infundibular stem caudally and extending anteriorly to the optic chiasm. Rahn concludes that a typical pars intermedia is absent in the chick. The time of differentiation of the acidophilic and basophilic cells in the various parts of the gland during embryonic life is described. Indirect evidence is presented that the embryonic pituitary gland does not exert any influence on the gonads during early development and that it is not responsible for the initiation of thyroid activity.

WYMAN, Boston.

DEVELOPMENT OF THE OPTIC NERVE IN THE RABBIT: MECHANISM OF FORMATION OF THE MEDULLARY SUBSTANCE OF THE OPTIC NERVE. DENKICHI MISHIMA, Ann. d'ocul. **175**:415 (May) 1938.

Mishima reports that in the first embryonic stage the optic glia cells are of two kinds, fibrillary astrocytes and oligodendrocytes. These cells become united by their protoplasmic processes, thus forming a network through which the neurofibrils pass. During the course of development the cell body becomes smaller, while the protoplasmic processes branch out and are transformed into the glial reticular fibers between the axis-cylinders. During this transformation the gliosomes are seen in the glial reticular fibers surrounding the axis-cylinders. At the end of the fetal period these granules show a strong reaction to silver nitrate and within a short time have the same microchemical reaction as myelin. Immediately after birth they proliferate and fuse to form the medullary substance.

This may indicate that the glia cells play an important role in the formation of the medullary substance, since they form first the gliosomes and axis-cylinders and then the fundamental substance of the myelin, which with the glia fibers receives other substances from the blood capillaries. BERENS, New York.

NERVE FIBERS IN THE SPINAL ROOTS IN CATS. KJELL KJELLGREN, Upsala läkaref. förh. **44**:247, 1939.

Kjellgren counted the number of nerve fibers in the spinal roots of an adult cat and of 2 other cats aged 22 and 4 days, respectively. He found in the adult cat 196,497 fibers in the right dorsal roots and 108,225 fibers in the right ventral roots, the ratio being 1.81 : 1. Owing to a technical error, a few spinal roots on the left side of the adult animal were destroyed. There were 180,619 fibers in the left dorsal roots and 101,567 fibers in the left ventral roots, with a ratio of 1.78 : 1. Considering the loss of a few roots, Kjellgren thinks that the number of fibers in the dorsal roots are about equal on the two sides while in the ventral roots there is a difference of about 6.32 per cent in favor of the right side. In the 22 day old animal he counted 166,124 fibers in the right dorsal roots and 87,334 fibers in the right ventral roots, the ratio being 1.90 : 1. In the 4 day old animal there were 120,380 nerve fibers in the left dorsal roots and 76,525 fibers in the left ventral roots—a ratio of 1.57 : 1. In the right roots there were 111,968 sensory fibers and 70,952 motor fibers, with a ratio of 1.58 : 1. A comparison of the counts in the 3 animals shows that the largest number of nerve fibers was in the adult and the smallest number in the youngest animal. The difference between the adult and the 4 day old animal was pronounced. The ratio of the dorsal to the ventral roots was about the same for the adult and the 22 day old animal, but was much lower for the younger cat. The author suggests that the larger number of nerve fibers in the adult animal must be due to postnatal increase. He rejects the possibility of an increase in the number of neurites in a single cell in postfetal life.

NOTKIN, Poughkeepsie, N. Y.

Physiology and Biochemistry

ACOUSTIC MOTOR REACTIONS, ESPECIALLY THE COCHLEOPALPEBRAL REFLEX. HANS STRAUSS, CARNEY LANDIS and WILLIAM A. HUNT, Arch. Otolaryng. **28**:941 (Dec.) 1938.

Experiments were made to note the reaction of a patient to a sudden loud sound. A pistol was fired, and the subsequent reactions were photographed with an ultraspeed camera, with 300 exposures per second. Parts of the reaction called the "startle pattern" have been termed by various otologists the "cochleopalpebral reflex," the "auropalpebral reflex," the "ocousticopalpebral reflex" or the "diffuse cochlear muscle reflex." It has been shown clearly that the immediate reaction to the sound is always composed of movements forming a typical pattern: shutting the eyes; characteristic distortion of the features; forward movement of the head; raising and drawing forward the shoulders; abduction, forward elevation and inward rotation of the upper parts of the arms; bending of the elbows; pronation of the forearms; clasping of the hands; contraction of the abdomen; forward movement of the trunk, and bending of the legs at the hips and knees. Some or all of the movements were always seen. The recorded experiments show definitely that the cochleopalpebral reflex invariably follows the sound stimulus in all persons having any remnant of hearing, except in epileptic persons and in "clouded" psychotic or unconscious persons. The literature contains reports that this reflex is not present in all persons with normal hearing. This is due to the methods of observation used. When a high speed camera is used the reaction is found in every case. The eye blink sometimes starts within 0.005 second and is over in

0.015 second after the exposure of the stimulus. Obviously, a reaction of such high speed must frequently be missed when direct observation is relied on. The reaction is always present in normal infants. No observations were carried out on infants under 7 days of age. Patients whose audiograms showed little hearing and who were unable to hear speech reacted to the test, showing that there was no relation between the degree of reaction and the amount of hearing. The degree of speed and intensity of reaction were probably determined by complicated circumstances, such as attention and tonus. The occurrence of the eye blink in persons who were practically deaf proved that it cannot be used to discover stimulation. No evidence was found to prove that the results were due to sensory stimulation of the cornea or of the external ear by air concussion.

HUNTER, Philadelphia.

THE RELATIVE INFLUENCE OF THE LOCUS AND MASS OF DESTRUCTION UPON THE CONTROL OF HANDEDNESS BY THE CEREBRAL CORTEX. GEORGE M. PETERSON and L. FRACAROL, J. Comp. Neurol. **68**:173 (Feb.) 1938.

To study the relative influence of the locus and mass of destruction of the cerebral cortex on the control of handedness, 27 ambidextrous rats were available. Handedness was determined by the use of Peterson's food situation. Animals were observed for seven periods before the operation, and a record was kept of the number of times each hand was used until a total of 50 reaches were taken on any one day. Destructions in all cases were made with thermocautery, chiefly in the frontal and occipital cortex. Seven days were allowed for recovery, after which the animals were observed for another period of seven consecutive days and then once a week for seven weeks. Sections of the brains were stained with thionine and reconstructions made of the lesions. From the reconstructions the area of destruction was computed with a planimeter. A small region in the contralateral frontal lobe is essential for the control of handedness by the cerebral cortex. The exact location varies from one animal to another. Injuries in the occipital and parts of the temporal region have no such effect on the use of the hands. The results of Peterson and Fracarol support the theory of localization in the cerebral cortex.

FRASER, Philadelphia.

DEVELOPMENT OF THE CEREBRUM OF AMBLYSTOMA DURING EARLY SWIMMING STAGES. C. JUDSON HERRICK, J. Comp. Neurol. **68**:203 (Feb.) 1938.

This paper continues the study of the development of the configuration of the cerebrum and the differentiation of its nerve fibers, as revealed by reduced silver preparations of 13 specimens of Amblystoma punctatum and 30 specimens of Amblystoma tigrinum, chiefly in early swimming stages. The early swimming stage is a brief critical period of rapid differentiation, during which the incipient locomotor activity of the S reaction stage is perfected and strengthened. Models of the brain at this stage showed a compact brain with cerebral flexures at their maximum. Parallel with progressive improvement in the efficiency of the swimming movements, cerebral differentiation advanced rapidly. The olfactory nerves enlarged rapidly; the optic fibers decussated and extended dorsad as far as the motor field of the ventral thalamus. The connections of these two nerves may exert a generalized, or nonspecific, influence on motility.

FRASER, Philadelphia.

EXPERIMENTS ON THE CORPUS STRIATUM AND RHINENCEPHALON. DAVID M. RIOCH and CHARLES BRENNER, J. Comp. Neurol. **68**:491 (June) 1938.

Opossums, rats, guinea pigs and cats were used for this study on the corpus striatum and rhinencephalon. In all animals, except 7 cats, unilateral cortical ablation was performed as a preliminary step. The cats, rats and opossums were then used for stimulation of the striatum. In the 7 cats the cortex was ablated

bilaterally. In the guinea pig the corpus striatum of one side was destroyed by freezing. The results of these stimulation experiments were essentially negative. Rioch and Brenner suggest that the striatum acts in conjunction with other systems of the forebrain and does not have autonomous function.

ADDISON, Philadelphia.

DORSAL ROOT REFLEXES. DONALD H. BARRON and BRYAN H. C. MATTHEWS, J. Physiol. **94**:26 P, 1939.

The observation of Tönnies that a volley of impulses arriving at the spinal cord by way of the dorsal roots is followed by a centrifugal discharge in the sensory nerve was reinvestigated. The centrifugal discharge followed a centripetal volley only when the cord was cooled; it was maximal at 33 C., detectible at about 36 C. and negligible at 38 C.

THOMAS, Philadelphia.

DORSAL ROOT POTENTIALS. DONALD H. BARRON and BRYAN H. C. MATTHEWS, J. Physiol. **94**:27 P, 1939.

Barron and Matthews studied the mechanism of the "dorsal root reflexes" described by Tönnies and shown by them to be dependent on a certain degree of cooling of the spinal cord. They relate the phenomenon to their previous observation that the arrival of impulses in the cord via the dorsal roots is followed by a slow central negativity which spreads peripherally by electrotonus. When the temperature of the cord is below normal this central negativity is accompanied by impulses which are conducted peripherally. "It appears that one-way conduction at the synapse is so delicately balanced that even a fall of temperature of a few degrees causes a partial failure."

THOMAS, Philadelphia.

MODIFICATIONS OF THE VESTIBULAR CHRONAXIAS DETERMINED BY ADMINISTRATION OF ALCOHOL IN ALCOHOLIC PERSONS. CASIMIR NIEMIROWICZ-SZCZYTT, Encéphale **2**:26, 1938.

Vestibular chronaxia was determined in 17 alcoholic persons either during abstinence or after the administration of from 10 to 50 cc. of alcohol from two to three hours after the last meal and in 9 nonalcoholic subjects after receiving alcohol. Skrzypinska found that from 12 to 22 milliseconds is the normal chronaxia for adults between 20 and 50 years of age, the same values as those given by Bourguignon. She found that the chronaxia is higher in subjects younger or older than the adult group. The author has shown that in nonpsychotic chronic alcoholic subjects at the beginning of abstinence the vestibular chronaxia remains normal or rises to values as high as 82 milliseconds. During acute alcoholic psychoses the chronaxia drops as low as 2.2 milliseconds, which corresponds to that of a child aged 1½ years, and rises again with the regression of acute symptoms. After prolonged abstinence the chronaxia remains below normal in most cases. After the ingestion of alcohol the chronaxia in all subjects undergoes three successive phases: diminution, increase to a value above the starting point and return to normal. In abstinent alcoholic persons the variations are greater than in control subjects. The effect is the same when alcohol is injected intravenously and when given through an esophageal catheter. In nonalcoholic persons administration of alcohol is followed by variations of the reaction time to sound, which parallel those of the vestibular chronaxia. In alcoholic persons, on the other hand, the variations are large and disordered and are often not parallel to those of the chronaxia. In certain cases of chronic alcoholism, even large doses of alcohol (50 cc.) are without effect on the reaction time to sound, while they produce the usual changes in chronaxia. The multiple choice reaction is slowed after the ingestion of alcohol.

LIBER, New York.

EFFECT OF BRIEF ELECTRIC SHOCKS ON COURSE OF EXCITATION IN SENSORY HUMAN NERVES. H. GATTNER, Arch. f. d. ges. Physiol. **240**:718, 1938.

The middle finger of test subjects was stimulated by a single and by a pair of electric shocks; the first of the paired shocks ("standard stimulus") was identical with the single shock; the second of the paired shocks ("test stimulus") was varied in intensity. The subject had to state whether a difference in intensity between the single stimulus and the paired stimuli was felt—in other words, whether the effect of the standard stimulus was changed by the test stimulus. With equal intensity of the standard and the test stimulus, the first excitation was followed first by a relative refractory period lasting 0.4 millisecond, then by an absolute refractory period of 0.3 millisecond and finally by a second relative refractory period of about 1 millisecond. If the test stimulus was stronger than the standard stimulus the absolute refractory period nearly disappeared, while it increased if the test stimulus was weaker than the standard stimulus. With very weak test stimuli the nerve was absolutely unexcitable for 1.3 milliseconds after excitation.

SPIEGEL, Philadelphia.

ACETYLCHOLINE IN PERIPHERAL NERVES. O. LOEWI and H. HELLAUER, Arch. f. d. ges. Physiol. **240**:769, 1938.

Acetylcholine extracted from peripheral nerves does not differ from the same substance extracted from the central nervous system, except that in the nerves no acetylcholine could be found that was not destroyed by esterase. The acetylcholine content of preganglionic (cholinergic) and of postganglionic (adrenergic) fibers of the cervical portion of the sympathetic chain was determined. In the postganglionic fibers only 15 per cent of the acetylcholine content of the preganglionic fibers was found. The optic nerve and the posterior roots of the spinal cord were free from acetylcholine. This is in agreement with the assumption of Dale that sensory fibers are not cholinergic. This suggests that the transmission of impulses from the sensory nerves to the ganglion cells of the central nervous system in reflex innervation is not mediated by the liberation of acetylcholine.

SPIEGEL, Philadelphia.

Neuropathology

DIABETES INSIPIDUS AS A SIGN OF METASTATIC INVOLVEMENT OF THE SUPRAOPTICOHYPOPHYSIAL SYSTEM. MITCHELL BERNSTEIN, MATTHEW T. MOORE and DAVID B. FISHBACH, Arch. Int. Med. **62**:604 (Oct.) 1938.

The authors report a case of both hematogenous and lymphogenous metastases of a bronchogenic carcinoma, the former producing diabetes insipidus by involvement of the posterior lobe of the pituitary gland and the latter resulting in involvement of the serous membranes of the abdominal and thoracic organs. In a review of 107 necropsy records of patients with diabetes insipidus, 63 per cent were found to have a neoplasm at the base of the brain or in the posterior cranial fossa. These involved more than one structure and hence were not of localizing value. In 14 per cent of the cases there was a discrete metastatic carcinomatous nodule limited to either the posterior lobe of the hypophysis or the infundibulum.

The case reported by the authors was that of a man aged 64 with diabetes insipidus. Postmortem examination revealed coronary arteriosclerosis; primary bronchogenic carcinoma of the left lung, with metastasis to the pleura, diaphragm, peritoneum and liver; metastatic bronchogenic carcinoma of the brain, posterior lobe of the pituitary body and infundibulum, and terminal petechial hemorrhages in the subthalamic region. The authors suggest that in the absence of conclusive evidence as to the etiologic factor in a case of diabetes insipidus a masked malignant process should be suspected and an effort made to establish a primary source. They also recommend that, as infundibulohypophysial involvement alone can cause polyuria, irradiation of the hypothalamicohypophysial area should be carried out empirically.

BECK, Buffalo.

OLIVO-PONTO-CEREBELLAR ATROPHY AND UNILATERAL INVOLVEMENT OF CRANIAL NERVE NUCLEI. CHARLES DAVISON and I. S. WECHSLER, J. Nerv. & Ment. Dis. **88**:569 (Nov.) 1938.

Davison and Wechsler report 7 cases which they classify as examples of olivopontocerebellar atrophy, with a complete pathologic study in 1 case. In this case, a man aged 30 had dizziness, vomiting, headaches and diplopia—symptoms which disappeared, leaving tremors and clumsiness in the hands and ataxic gait. Twenty months after the onset facial paralysis, tinnitus and deafness appeared on the right side, with dysarthria and dysphagia. Exploration revealed only moderate injection of the ninth, tenth and eleventh cranial nerves. Two and one-half years after the onset neurologic examination revealed a marked degree of cerebellar ataxia in all extremities, particularly on the right, with adiadokokinesis, rebound phenomenon and staggering gait. In addition, there was partial or complete involvement of all the cranial nerves on the right side, from the third to the tenth, inclusive. Studies of the spinal fluid, blood and urine gave normal results, as did roentgen examinations of the skull. The patient died four years after the onset. Degenerative changes were seen only on the right side, implicating the cerebellar cortex, white matter and dentate nucleus and all three cerebellar peduncles. The posterior longitudinal bundle, the inferior olive and the pontile and arcuate nuclei were all involved, and degenerative changes were observed in the nuclei of all the cranial nerves on the right side, from the third to the tenth, inclusive. In the areas of degeneration there were compound granular cells, increased numbers of glia cells, advanced demyelination and numerous amyloid and psammoma bodies. In the cerebellar cortex the molecular, Purkinje and granular layers were extensively involved. The Purkinje cells were almost absent in many regions, and when present showed chromatolysis, shrinking or pyknosis. No evidences of "inflammation" or of vascular or neoplastic disease were seen.

In the other 6 cases only clinical studies were made. Two patients were brothers, in whom the disease began at the age of 27 and 41, respectively, and whose father had become ataxic at 55. Both brothers showed evidences of cerebellar disturbance, and 1 had also diminution of position and vibration sense in the lower extremities, with pathologic plantar responses on both sides. In these 2 cases Davison and Wechsler consider that Friedreich's disease was excluded by the late onset and the absence of clubfoot and scoliosis. In the other 4 patients the onset was at the age of 45, 47, 43 and 50, respectively. Two of these patients were addicted to alcohol. All showed advanced signs of cerebellar disturbance, without evidences of disease of the spinal cord. Nystagmus was present in 3 of the 4 cases.

MACKAY, Chicago.

PATHOLOGY OF HUNTINGTON'S CHOREA. THEODORE T. STONE and EUGENE I. FALSTEIN, J. Nerv. & Ment. Dis. **88**:602 (Nov.); 773 (Dec.) 1938.

Stone and Falstein report the clinical and pathologic features of 6 cases of chronic degenerative hereditary chorea. In all but 1 case there was a history of the disease in other members of the family. The clinical syndrome observed in all cases was stereotyped and included choreic movements, progressive dementia, emotional instability and usually some delusional aberrations. The pathologic changes were practically identical in all 6 brains. There was generalized atrophy of the brain, especially in the frontal and precentral regions and to a lesser degree elsewhere in the cortex. In these areas the ganglion cells of the third and fourth layers of the cortex were shrunken and distorted. Satellitosis and neuronophagia were occasionally seen, but there was no gliosis. There was marked atrophy of the putamen and candate nucleus, with pronounced cellular deficit. The few remaining cells were shrunken and distorted. The globus pallidus was also slightly atrophic. Marked astrocytic gliosis, proportionate to the destruction of ganglion cells, was present in the striatum. The lateral ventricles were dilated, and

the leptomeningeal spaces and sulci were distended, especially in the frontal and parietal lobes, in all cases. In 2 cases there was moderate arteriosclerosis, and in 1, doubtful degeneration of the ganglion cells of the thalamus. Stone and Falstein conclude that Huntington's chorea is a hereditary degenerative disease due to premature atrophy of the cells of the cerebral cortex and neostriatum. From a study of the literature, they believe that chronic progressive nonfamilial chorea is a disease with different pathologic characteristics and is due to encephalitis, meningoencephalitis or hemorrhage.

MACKAY, Chicago.

HISTOLOGIC CHANGES IN THE BRAIN IN MONGOLISM. A. MEYER and T. B. JONES, J. Ment. Sc. **85**:206 (March) 1939.

Meyer and Jones examined histologically the brains in 15 cases of mongolism and observed definite changes in 10 of them. These changes consisted mostly of widespread proliferation of the fibrous glia, which often was not accompanied by corresponding changes in the myelin and cells. It is shown that the observations are not likely to represent the pathologic substrate of mongolism. They throw light, however, on the interpretation of the changes reported by previous writers. Most of these investigators discussed the changes in the brain as an expression of the pathologic process underlying mongolism. Reserve is necessary in submitting far reaching conclusions. The authors' material, which represents a wide variation in length of life, shows that relatively recent changes may be seen even in persons who die in the third decade of life. It is likely, therefore, that all such changes must be regarded as incidental to the pathologic changes in mongolism. It may well be that the incidence of pathologic changes is greater in mongolism than in other conditions, owing to the peculiar constitution of the patient. One might even assume that the same functional abnormality underlying mongolism produces also the histologic changes, which, though constant, would obtain a certain significance as an indicator of the pathogenesis of mongolism, but this is at present purely speculatvie. Enough is not known about the reaction of the brain to bodily diseases, especially in infancy and childhood, and therefore it cannot be decided whether this reaction is more severe in persons with mongolism than in other defective and in normal persons. Systematic control will be necessary before a real appreciation of the cerebral changes in mongolism will be possible. There is no consistent correlation between the size of the brain stem and the degree of glial scarring, though it is conceivable that the glial scarring, if severe, may contribute to the smallness.

J. A. M. A.

PATHOANATOMIC CHANGES IN THE CENTRAL NERVOUS SYSTEM IN INFANTILE ACRODYNIA. J. RUESCH, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:361, 1938.

Studies of the pathoanatomic picture and pathogenesis of acrodynia have in general been inadequate. Ruesch reports the case of a boy aged 22 months who lost appetite and began to vomit frequently three months before admission to the hospital. After an attack of acute cystitis a month later, he became irritable and apathetic. A rubeoliform rash appeared on the trunk, and the hands and feet became reddened, cold and cyanotic. Pyoderma with crusting, which was noted on the occasion of the first examination, became aggravated; subcutaneous abscesses developed, and the child died a week after admission.

Gross examination of the central nervous system revealed nothing abnormal. Though various stains and impregnation methods were employed, no significant alterations of the ganglion cells could be demonstrated. Throughout the brain and spinal cord blood vessels with dilated adventitial lymph spaces, surrounded by clusters of glia cells, were occasionally seen. Though the cells were mainly of the oligodendroglia variety, a few were of the plump, or gemästete, cell type. There was considerable persistence of the subependymal germinal layer, and in the immediate neighborhood of the entire ventricular system were seen germinal

centers containing oligodendroglia and macroglia cells, in addition to less mature forms. Precapillaries surrounded by an increased number of oligodendroglia cells were seen throughout the same area; they were most numerous, however, in the corpus callosum and anterior commissure. Indications of receding myelination gliosis were also noted. No changes were noted in the lateral horns of the spinal cord or in the sympathetic ganglia.

The view is expressed that the changes seen in the blood vessels are not specific for acrodynia, but are attributable rather to the infection which complicated the disease in its later course. Significance is attached, however, to the persistence of the subependymal germinal layer and the germinal centers, both of which usually disappear before the eighth month of life. It is suggested that the retarded development of the brain may have rendered it more susceptible to the action of certain endogenous or exogenous noxae. With reference to the increased number of perivascular oligodendroglia cells, the view is expressed that immature perivascular cells may react to noxious agents in this manner. The common occurrence of acrodynia in the second and third year of life is emphasized.

DANIELS, Denver.

Psychiatry and Psychopathology

THE PERSONALITY TYPE OF PATIENTS WITH TOXEMIAS OF LATE PREGNANCY. LYLE G. MCNEILE and ERNEST W. PAGE, Am. J. M. Sc. **197**:393 (March) 1939.

McNeile and Page studied eclamptogenic toxemias in 148 women in an obstetric ward. Ninety-seven patients presented persistent elevation of blood pressure above 140 systolic or 90 diastolic and were placed in a "hypertensive group." The incidence of a familial history of hypertension in group 5 (11 patients with arteriolar essential hypertension complicating pregnancy) was three times that in the control group of 51 normal pregnant women. In group 2 (16 patients with chronic vascular-renal disease) and in group 4 (8 patients with hemorrhagic Bright's disease) the incidence was also increased. Over 90 per cent of the 11 patients in group 5 were high strung, easily excited within themselves, unusually sensitive, easily worried, unusually shy or unusually active physically. Women with preeclampsia, eclampsia or nephritis did not differ in their personality traits from normal pregnant women. Essential hypertension seems to be associated with a "hypertensive personality." The results suggest that there is a relationship between the nervous system and the mechanism of hypertension in cases of essential hypertension, which is not present in the toxemias of late pregnancy.

MICHAELS, Boston.

MYXEDEMATOUS HYPOTHYROIDISM ASSOCIATED WITH PSYCHOSIS. A. SIMON, Illinois M. J. **75**:66 (Jan.) 1939.

Although the diagnosis of psychosis with myxedema is rare, 3 cases have been observed at the Elgin State Hospital during the last few years. Simon reports these cases in order to emphasize some of the factors which may modify or determine the reaction pattern and course of the psychosis. The variations in the reaction patterns in these cases are attributed to differences in the hereditary, constitutional and environmental background, as well as to organic conditions. The author believes that young persons in whom myxedema develops and who possess a schizoid personality are prone to have schizophrenic psychoses. In elderly patients with involutional and cerebral arteriosclerotic changes an organic psychosis, characterized by a loosely constructed paranoid delusional system with confusion and vague hallucinatory experiences, is apt to develop. Appropriate thyroid therapy may improve the physical and possibly ameliorate the mental condition.

J. A. M. A.

COMPARATIVE STUDY OF PSYCHOSES AMONG NEGROES AND WHITES IN THE NEW YORK STATE PRISONS. S. C. KARLAN, Psychiatric Quart. **13**:160 (Jan.) 1939.

Karlan studied all patients first admitted to the Dannemora State Hospital from the New York state prisons from June 30, 1928 to June 30, 1938. These included 687 white persons and 188 Negroes. During these ten years 25,538 white persons and 5,494 Negroes were committed to the institutions of the New York State Department of Correction. From his observations the author concludes that the incidence of psychoses in the general population is higher among Negroes than among white people. In the New York state prisons, Negroes and white prisoners are in a similar cultural and economic environment. The incidence of functional psychoses among Negro inmates is about the same as that among white prisoners. Negroes have therefore no racial predisposition to mental disease. The high incidence of mental disease among them is due probably to cultural, social and economic causes. The incidence of psychoses among prison inmates is from five to ten times that of the general population. This is due chiefly to the inherent constitutional instability of the criminal group.

J. A. M. A.

THE USE OF AUTOMATIC DRAWING IN THE INTERPRETATION AND RELIEF OF A STATE OF ACUTE OBSESSIONAL DEPRESSION. MILTON H. ERICKSON and LAWRENCE S. KUBIE, Psychoanalyt. Quart. **7**:443, 1938.

Erickson and Kubie describe the case of a girl aged 24 who had been unhappy and uneasy in her social relations, and had been worried, unhappy and depressed for about a month. As far as she knew no personal problem was troubling her. Through the use of automatic drawing, which she had begun at about the time when her depression started, the patient suddenly became conscious that she must have been aware for about two months that her father was having an affair with her best friend. With this knowledge she broke off her relationship with the girl and forced her to stop her visits to the house. The patient immediately felt well, stopped her automatic scribbling and apparently has remained well since. The authors think that this case raises several technical challenges. Even the most skilful use of orthodox psychoanalytic technic could not possibly have uncovered the repressed awareness of the father's liaison in a few sessions. The automatic drawings, as a method of communication, have a close relation to the psychoanalytic method of free association. In free association the single vehicle of speech is used by both the conscious and the unconscious part of the personality. In this case the therapeutist instructed the patient to use speech to express her conscious ideas and to leave the expression of her unconscious impressions to her automatic drawings. In this he widened the gap between the conscious and the unconscious part of the psyche, and so perhaps secured unconscious communications more easily.

PEARSON, Philadelphia.

CHARACTER AND SYMPTOM FORMATION: PRELIMINARY NOTES ON PATIENTS WITH HYPERTENSION, RHEUMATIC AND CORONARY DISEASE. FLANDERS DUNBAR, Psychoanalyt. Quart. **8**:18, 1939.

Since the majority of patients with somatic disorders have neurotic characters rather than full-fledged psychoneuroses or psychoses, Dunbar made observations from the standpoint of character formation on 1,300 patients admitted routinely to the hospital with cardiovascular disease, diabetes and fractures and on selected patients with gastric ulcer, allergy and cutaneous lesions. The majority of patients were studied by means of short time contacts, particular attention being paid to four situations: (1) somatic makeup, including constitution, heredity and organ conditioning; (2) focal conflict and specific psychologic conditioning; (3) fundamental character structure (genital and pregenital), strength of ego and nature and strength of its defenses, that is, the "characteristic" ways of handling difficulties or of reacting to stress and strain, expressed both in physiologic and in

psychologic terms, and (4) possible adventitious factors, such as exposure or economic handicaps. Selected patients in each group were analyzed for the better understanding of their deeper psychologic makeup.

Most patients with fractures have a focal conflict over submission to authority and have marked hostility. They express this in action, so that they tend to hurt others and themselves accidentally. Their tension is of a jerky, spastic type. If this conflict is resolved, the tendency to accidents decreases. Ninety per cent of these patients had stern parents, both of whom lived into the patient's adolescence. Most hypertensive patients also have the same focal conflict as do patients with fractures, but they tend to inhibit their actions, so that they have generalized tension involving both the skeletal and the smooth musculature. Patients with dyspnea and palpitation show phobias and prominent conversion mechanisms. The mechanism is sometimes genital, as in hysteria, but more often is pregenital, tending toward that characteristic of the asthmatic patient, but there seems not to be such a marked prominence of anal material and oral character organization, on the one hand, and of the tendency to act out aggression, on the other, as is found in asthmatic patients. Even when the dyspnea and palpitation have as their basis rheumatic heart disease and myocardial damage, these symptoms are much more marked in persons who have been exposed to parents or friends with such symptoms. The symptom complex has a definite significance to these patients, usually in terms of the Oedipus situation and of the tendency to identification with the mother, together with the need to break away and take revenge. Dreams of smothering and a tendency to claustrophobia are characteristic. The group of patients with cardiac pain, either in addition to or apart from dyspnea and palpitation, seem to show a still greater tendency to anxiety hysteria. It may be noted in passing that although these patients may have either agoraphobia or claustrophobia, the great majority have claustrophobia and tend to avoid acting out their fantasies. Anxiety neurosis is a complicating factor of great physiologic importance.

Patients with arthritis have little tendency to impulsive action, but have a rich fantasy life. They show a tendency to symbolization of the sites of the pain. They associate the arthritic pain with masturbation and restraint or punishment, and the focal conflict is related to the sexual role; i. e., girls are inclined to be tomboyish and boys to be passive.

Patients with anginal pain, whether as the result of organic heart disease or as a neurotic symptom, present a complex picture in which the vascular and muscular spasm is related to repressed hostility. They show also a prominent sense of guilt and tendency to self punishment.

Dunbar states emphatically that she does not intend to relate the characteristics enumerated exclusively to the somatic syndromes in question, but wishes merely to note that they have been found in patients with such disorders in varying degrees of prominence as one group is compared with the other. She concludes that if one hopes to cut down the ever increasing bulk of chronic illness and to deal adequately with the diseases which are now major causes of morbidity and mortality, one must institute treatment in the phase of minor illness; the treatment should as nearly as possible be etiologic in both its somatic and its psychic aspect.

PEARSON, Philadelphia.

THE IMPEDANCE ANGLE AND ITS RELATION TO THYROID TREATMENT IN MENTAL DISORDER. WILLIAM SARGANT, RUSSELL FRASER and M. A. B. BRAZIER, J. Ment. Sc. **84**:255 (March) 1938.

The authors were inspired in this work by the experience of Gjessing, who demonstrated the efficacy of thyroid medication in certain carefully selected cases of mental disease. He found that in the intervals between attacks the patients showed abnormalities suggestive of slight hypothyroidism. He found also that during the quiescent intervals there gradually developed retention of nitrogen; when the nitrogen retention reached an individual maximum a catatonic attack occurred, during which the nitrogen excess was excreted and the patient again

returned to comparative normality. Gjessing found that administration of thyroid could prevent the accumulation of nitrogen by these patients and could stop the attacks of catatonic excitement and stupor. He controlled his studies with accurate readings of the basal metabolic rate.

The authors point out that in most hospitals for mental disease therapy cannot be controlled with careful estimation of the basal metabolic rate, and hence they suggest the simplified procedure of determination of the impedance angle. They report scattered observations in 62 unselected cases. Determination of the impedance angle is carried out as follows: The patient sits on a chair with each arm immersed in a separate arm bath containing 10 liters of a 1 per cent solution of sodium chloride, at a temperature of about 25 C. When the arms are immersed, an alternating current (20,000 cycles per second), of sufficiently low intensity to be imperceptible to the patient, is led through the subject into a modified Wheatstone bridge circuit. The impedance offered by the patient to the current can be balanced on the bridge by adjusting a variable condenser and a variable resistance, the instrument being designed to give direct readings of the impedance angle. It has been shown that the results obtained are unaffected by slight movements on the part of the patient or by emotional alterations due to the test. No preparation of the patient by resting or fasting is necessary, and the only cooperation required of the patient is that he keep his arms still in the water.

It has been shown that the impedance angle of the normal person remains constant over long periods. The normal values were found to be 0 ± 2.2 (standard deviation, 12.8) for men and 0 ± 1.7 (standard deviation, 10.1) for women.

The results indicate that maximum improvement was obtained in cases in which response to thyroid medication coincided with the attainment of an impedance angle of about 20. Improvement occurred in cases of schizophrenia in which there was a marked depressive component and in cases of depression forming a phase of manic-depressive psychosis.

KASANIN, San Francisco.

DISTURBANCES OF SOMATIC FUNCTIONS IN CATATONIA WITH A PERIODIC COURSE, AND THEIR COMPENSATION. R. GJESSING, J. Ment. Sc. **84**:608 (Sept.) 1938.

Gjessing finds that there is a distinct periodicity in the nitrogen balance in some cases of catatonia. When stupor or excitement sets in at the beginning or end of the negative phase of nitrogen balance, he can stop the mental and physical disturbances by thorough emptying of the nitrogen store with thyroxin and thereafter prevent retention by suitable doses of thyroid.

It must be emphasized that in this small, carefully selected group of cases it is possible by these means to compensate for a functional deficiency, but not to effect a cure. If retention is not prevented the nitrogen store is filled again during the course of weeks or months, and suddenly the catatonic stupor or excitement sets in as before and is repeated in series. However, there are cases in which after the smallest effective dose of thyroid has been used for some time, the patient's own thyroid gland has been influenced and has been able to take over the entire work. As a result, without medication and on an ordinary diet the patient has been free from attacks for years. In young persons and in cases of recent onset this result is easier to attain than in older patients and in more chronic states, but even here the possibility of functional breakdown remains, and in this sense the patient is not cured. It can be said further that without thyroid medication in these cases remissions would not have occurred.

KASANIN, San Francisco.

SOME GENETICAL PROBLEMS IN MENTAL DEFIENCY. L. S. PENROSE, J. Ment. Sc. **84**:693 (Sept.) 1938.

The few diseases in which hereditary mental defect has been clearly demonstrated are found in idiots and imbeciles. Much less is known about the hereditary factors which underlie feeblemindedness. In all grades of mental defect, heredity

plays an approximately equal part, but the degree of dominance of the hereditary factors is different in the various grades. The defects in idiots and imbeciles are often recessively determined or are due to fresh mutation, and are less obviously hereditary than those in simpletons, who, like normal persons, owe their mental grade to the interaction of dominant additive factors. Environmental influence may be the only cause in comparatively rare cases. The external circumstances, indeed, are likely to be even more important in mild than in severe mental deficiency, for their effects may make the difference between certifiability and normality.

KASANIN, San Francisco.

SHORT-DISTANCE PROGNOSIS OF SCHIZOPHRENIA. E. GUTTMANN, W. MAYER-GROSS and E. T. O. SLATER, J. Neurol. & Psychiat. **2**:25 (Jan.) 1939.

For a better evaluation of the prognosis in schizophrenia with the modern insulin or metrazol therapy, it is necessary to obtain information on the course of the disease without active treatment. For this purpose the authors have investigated the status of a group of 188 schizophrenic patients from two to four years after their discharge from the Maudsley Hospital. The material consisted of a group of cases in which the prognosis was favorable and in which the illness was of less than a year's duration; the ages were below 45 years, and the diagnosis was not doubtful. The results disclosed that about 50 per cent of the patients were either in hospitals for mental disease or were invalids at home; 8.3 per cent had recovered with social defect, and 34.5 per cent had made total or social recoveries. The prognosis was found to be better for women than for men. The factor of age could not be determined, but the studies suggested that the prognosis was better in patients whose illness began before the age of 20.

MALAMUD, Ann Arbor, Mich.

CORRELATIONS OF COLLOIDS IN THE PLASMA OF SCHIZOPHRENIC PATIENTS. S. SCHRIJVER-HERTZBERGER, Encéphale **1**:181, 1938.

The following features of the blood were studied in schizophrenic and other psychotic patients: (*a*) the quantity of fibrinogen, globulin and serum-albumin; (*b*) the total albumin content; (*c*) the sedimentation rate of the erythrocytes, and (*d*) the stability of the colloids. Destruction of body proteins occurs in many diseases; its best known index is the accelerated sedimentation of erythrocytes. In most internal diseases, such as tuberculosis, this is accompanied by instability of the plasma colloids, as evidenced by increased flocculation of the plasma by addition of electrolytes. In certain cases of schizophrenia, on the other hand, accelerated sedimentation is accompanied by diminished flocculation, demonstrating stability of the plasma colloids. This anomalous combination has been observed in atypical, relatively curable forms of schizophrenia, in cyclic forms of the disease during regression of an attack, at the end of treatment by prolonged narcosis and in arrested dementia paralytica. Stability of colloids is believed therefore to indicate a favorable prognosis in schizophrenia. In cases in which prolonged narcosis did not result in improvement stability of colloids did not occur. The accelerated sedimentation rate with colloid stability is rare in cases of neurasthenia, epilepsy, manic-depressive psychosis and cerebral arteriosclerosis. It is found frequently in cases of tumors of the brain and cerebral syphilis as well as of schizophrenia.

LIBER, New York.

Diseases of the Brain

CEREBRAL PARATUBERCULOSIS. R. C. COHEN and W. BURTON WOOD, Lancet **2**:1344 (Dec. 10) 1938.

Cohen and Wood call attention to a new clinical syndrome of the central nervous system: acute exudative meningitis, transient and benign, which occurs in young persons and children with pulmonary tuberculosis. Five cases are

reported in which the patients ranged in age from 6 to 20 years. The predominant features of this condition are headache, lethargy, fever, sluggish pupils, diminution or absence of the quadriceps reflex, variable rash, elevation of the spinal fluid pressure, clear spinal fluid, without cells or increase in protein, and recovery in from seven to fourteen days. The absence of irritative meningeal signs distinguishes it from the acute aseptic meningitis of Wallgren. The authors suggest the possibility that the condition is an allergic reaction to the "tuberculous virus."

KRINSKY, Boston.

TRAUMA AND INTRACRANIAL TUMORS. L. B. COX, M. J. Australia **1**:256 (Feb. 18) 1939.

Of a series of 150 consecutive cases of proved intracranial tumor, Cox found that trauma appeared to have been related to the onset of symptoms in 4 cases (2.6 per cent), or possibly in 5 (3.3 per cent). In 2 of these, intracranial tumors were almost certainly present at the time of the injury. In 1 the microscopic study strongly suggested that the injury had caused focal changes within the tumor, about which a considerably enhanced rate of division of the neoplastic cells was taking place. In 2 cases tumors were observed in the regions of known sites of injury of a fairly severe grade. It is likely that in 1 of these the tumor followed the injury; in the other it is possible that the tumor followed the injury, for although a long period elapsed between the onset of symptoms and the injury, the tumor was of a slowly growing type. It is thought that a brain containing a tumor is more likely to be injured by a blow than a normal brain. This seems to be true also for areas of the central nervous system containing simple malformations. A brain already the seat of inflammation would certainly have an enhanced susceptibility to injury. This may explain the apparently traumatic origin of many of the inflammatory and degenerative conditions of the central nervous system.

J. A. M. A.

CEREBRAL TUBERCULOMAS. C. VINCENT, Ann. méd.-chir. **3**:151 (May) 1938.

Vincent reports the clinical and pathologic observations in 34 cases of tuberculoma of the brain. These cases were found in a total of 1,348 cases of histologically verified tumors and represent 2.5 per cent of all cases of tumors observed. In 18 cases the tuberculoma was localized in the cerebellum; in 10, in one cerebellar hemisphere; in 5, in the vermis, and in 3 there were multiple tuberculomas of the cerebellum. In 10 cases the tuberculomas were cerebral; in 3 they involved the brain stem, and in 3 they occurred in both the cerebrum and the cerebellum. Tuberculomas were more frequent in the right hemisphere than in the left. With the exception of 2 cases, the cerebral tuberculomas were immediately under the arachnoid, but were not adherent to the dura. In the cerebellum the tuberculomas were most often adherent to the dura, and in several cases, to the tentorium. The macroscopic and microscopic structure was identified with that in tuberculomas elsewhere. Contrary to previous observations, the majority of the tuberculomas were in adults. In 14 cases the patient was under the age of 20, and in 20 cases, over 20. Twenty-eight of the patients in this series were operated on. The 6 patients who were not operated on had advanced pulmonary tuberculosis, and the syndrome of intercranial hypertension developed terminally. In the 9 cases of cerebral tuberculoma in which operation was performed there were 6 cures, 4 of which followed complete removal of the growth and 2 decompression. Three of the patients with tuberculoma of the cerebellum who were operated on were cured. In the other cases, some patients died at the time of the operation, some died of tuberculous meningitis following operation and the remainder died of systemic tuberculosis.

DE JONG, Ann Arbor, Mich.

IMPORTANCE OF FACIAL PARALYSIS IN LOCALIZATION OF CEREBRAL TUMORS. Y. PIETTE, Bruxelles méd. **19**:572 (March 5) 1939.

Piette maintains that facial paralysis is observed frequently in the evolution of cerebral tumors. In the examination of 30 patients presenting the syndrome of intracranial hypertension it was observed twenty-one times. In 1 case it was due to a chronic subdural hematoma, and in 3 cases arachnoiditis existed. In the other cases there existed tumors of the cerebral hemispheres or of the posterior fossa. Facial paralysis was accompanied by signs of involvement of the homolateral pyramidal tract in 5 cases (frontoparietal tumor, tumor of the thalamus, craniopharyngioma, tumor of the rolandic area and tumor of the fourth ventricle). The facial paralysis was of the peripheral type in only 4 cases; the cases in question were those of acoustic neurinoma, arachnoiditis of the posterior fossa, tumor of the fourth ventricle and a meningioma adhering to the tentorium cerebelli, passing between the cerebellar tentorium and the cerebral peduncles and then passing under the tentorium into the posterior fossa. This tumor was accompanied by homonymous hemianopia on the left side and by the syndrome of the right cerebellopontile angle. Facial paralysis of the peripheral type is an important symptom of tumors of the acoustic nerve and of the cerebellopontile angle. Facial paralysis of the central type is frequently encountered in cases of cerebral tumors of various locations. When the paralysis is an isolated symptom it permits only the determination of the site of the tumor. On the other hand, it assumes great importance if it is accompanied by early psychic disturbances or by motor aphasia. In these cases it indicates almost with certainty a tumor of the frontal lobe.

J. A. M. A.

FACIAL NAEVUS FLAMMEUS, CEREBRAL ANGIOMA AND GLAUCOMA. D. MANOLESCO, D. LAZARESCO and D. VINTILESCO, Rev. d'oto-neuro-opht. **16**:664 (Dec.) 1938.

The classic, symptomatic triad of Schirmer-Sturge-Weber's disease—naevus flammeus, glaucoma and cerebral symptoms with intracranial calcifications—is extremely rare. Only 68 cases have been reported, in all of which nevus and glaucoma were associated, and in some of them cerebral angioma was surely or probably present. The facial nevus may be bilateral; it is usually unilateral and is on the same side as the glaucoma. Bilateral glaucoma is exceptional. The location of the intracranial angioma varies, resulting in a multiplicity of neurologic symptoms: epilepsy, hemianopia, the adiposogenital syndrome, imbecility and psychic disturbances. The authors report a typical case in which the nevus involved both sides of the face, the mucosa of the mouth and palate and the right eyelid, conjunctiva and choroid. An absolute glaucoma without buphthalmia, associated with deep excavation of the disk and blindness, was present in the right eye. The nervous manifestations were epilepsy in infancy, a mental depressive state, cerebellovestibular disturbances (nystagmus, pendular reflexes, deviation to the left) and left homonymous hemianopia. A roentgenogram showed a calcified vessel in the right occipital region. Fourteen cases in which the enucleated eyeball was examined histologically were found in the literature. In only 3 of these was there no intraocular vascular disease. Only when there has been complete anatomic examination of serial sections of the entire choroid may it be determined that there are no angiomatous changes present. If all patients with naevus flammeus of the face were subjected to a complete ophthalmologic and neurologic examination, the glaucoma might be arrested or retarded in its development and the associated intracranial angioma submitted to treatment.

DENNIS, San Diego, Calif.

LITTLE'S DISEASE AND EPILEPSY. M. BIRO, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:1, 1938.

Biro selected from a group of 35 cases in which there were various types of cerebral diplegia, paraplegia and hemiplegia of childhood 10 in which convulsive seizures had been recorded. In 3 cases the cerebral palsy became manifest at the end of the first year, during the course of which the children had had one or two

convulsions. Seizures preceded the appearance of signs of cerebral involvement by a few months in the fourth case and continued to recur with the progress of the disease. The interval between the onset of convulsions and that of the paralysis was only a few days in 2 cases, but whereas in 1 of these the attacks ceased to recur, in the other the patient later became subject to localized tonic spasms. In another case there were one convulsion at the onset of the cerebral palsy and another a year later. Convulsions preceded other symptoms by a few months in 3 cases and recurred later, but in only 1 case did they continue to recur in the later course of the disease.

Biro expresses the view that convulsions in Little's disease generally appear in the early stages. In most cases, including those in which there are a series of attacks, the seizures cease sooner or later, although prognosis is difficult in this respect even after prolonged observation. In addition to the anatomic changes, certain physiologic factors, chemical or physical, probably play a part in the genesis of the convulsions. There is no correlation between the type of cerebral palsy and the frequency of epileptic attacks, nor are mental disturbances more frequent in patients who have convulsions than in those who do not. Control of the seizures is always important; in cases in which the evidence of cerebral damage is slight it is the main task.

DANIELS, Denver.

FAMILIAL RUDIMENTARY MULTIPLE SCLEROSIS AND HEREDITARY ANOMALIES OF THE ABDOMINAL REFLEXES. HEINZ WILLACH, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:392 (Jan.) 1939.

Willach reports on two families with multiple sclerosis. The first family consisted of 5 siblings, 2 of whom had a definite mild form of multiple sclerosis of long standing; the other 3 members showed significant diminution of the abdominal reflexes. Tremor of the hand and temporal pallor were noted in persons who did not have definite multiple sclerosis. The second family presented a less definite picture. Two brothers had no abdominal reflexes, and in 2 others these reflexes were easily exhaustible or not elicitable in one quadrant. Three maternal uncles and aunts, the father and his 2 sisters had abnormal abdominal reflexes.

The abdominal reflexes were studied in the relatives of 105 patients with disseminated sclerosis, in 101 relatives of tabetic patients and in the relatives of 200 persons used as controls. They were found to be abnormal in 11.9 per cent of the multiple sclerosis group, in 1.7 per cent of the control group and in 2.1 per cent of the tabetic families. These abnormalities of the abdominal reflexes occur with significantly greater frequency in the relatives of patients with multiple sclerosis. The difference in the frequency of such anomalous reflexes in the multiple sclerosis and in the control group is more than three times the probable error. These observations are much in favor of the theory that genetic factors are of etiologic importance in multiple sclerosis.

SAVITSKY, New York.

CAROTID SINUS AND ITS ROLE IN CERTAIN HEADACHES AND VASCULAR PHENOMENA IN THE HEAD. A. J. HEYMANOWITSCH, Acta med. U.R.S.S. **1**:74, 1938.

Pressure on the carotid sinus results in reflex pain in the temporal region. The carotid sinus may be a cause of headaches, since the sinus is connected with the temporal region of the cranium through the second branch of the trigeminus nerve. There is a rich network of neurons connecting the carotid sinus with the second and third divisions of the trigeminus nerve, as well as with the ninth, tenth and eleventh cranial nerves. Heymanowitsch describes the "carotid-temporal syndrome," which is occasionally observed in cases of syringomyelia, petit mal and neuralgias of the maxillary nerve. In most cases the sinus is not the primary cause of temporal headaches, as the vascular system plays an important role in such conditions. He points out, however, that many headaches of unknown origin can be explained by involvement of the carotid sinus.

KASANIN, San Francisco.

Treatment, Neurosurgery

SULFANILAMIDE IN THE TREATMENT OF EXPERIMENTAL STREPTOCOCCIC MENINGITIS. PAUL E. ADOLPH and JOHN S. LOCKWOOD, Arch. Otolaryng. **27**:535 (May) 1938.

White rats were inoculated with Streptococcus haemolyticus injected into the dura mater. A 10 per cent emulsion of sulfanilamide in 1.6 per cent acacia was administered for five days by a tube passed into the stomach. It was found that the concentration of sulfanilamide in the spinal fluid is only slightly less than that in the blood. It is excreted rapidly by the kidneys. Almost all the rats, both of the control and of the treated groups, showed at some time definite signs of meningismus. Autopsy was done immediately after death. When sulfanilamide was given once a day the survival rate was only 25 per cent, and the average length of life of animals which died was two and a third days; the latter figure was about the same as for the control group. When the same amount of sulfanilamide was given in divided doses the survival rate increased to 57 per cent, and the average length of life of those that died, to six and eighty-three hundredths days. These facts conform to general clinical experience that repeated doses at short intervals, preferably every four to six hours, yield the best results. The clinical progress of the disease also changed with more frequent administration of the drug. On the third day the rats receiving the drug twice daily became more lively and when released from the cage ran around actively on the table, whereas by that time most of the control animals were dead. Surviving animals were watched for two months, and none died of delayed infection. In treated animals the exudates were free from cocci. The organisms, when present, were confined to a localized abscess or were accompanied by an increased infiltration with phagocytes. There was no striking increase in phagocytosis in the treated animals. It was suggested that the streptococci were not capable of multiplying in unrestricted fashion in the treated animals, as they seemed to do in the controls. In 1 case the streptococci presumably became virulent again after the sulfanilamide was withdrawn. The best results are obtained by oral administration of the sulfanilamide. It is important to maintain an adequate level by oral and subcutaneous administration.

HUNTER, Philadelphia.

TREATMENT OF PAIN IN THE FACE BY INTRAMEDULLARY TRACTOTOMY. G. E. ROWBOTHAM, Brit. M. J. **2**:1073 (Nov. 26) 1938.

Three patients with pain in the face were treated by section of the pain fibers in the descending tract of the trigeminal nerve. The operation requires exposure of the medulla. Just below the level of the most inferior root of the vagus nerve a transverse incision, about 4 mm. long and 3.5 mm. deep, is made in the tuberculum cinereum. This procedure produces analgesia of the face without anesthesia. There is no disturbance of the muscles of mastication and no loss of tear secretion. Two of the patients had trigeminal neuralgia involving the forehead. One had migraine. Immediate relief was obtained in each instance.

ECHOLS, New Orleans.

NARCOSIS THERAPY. R. D. GILLESPIE, J. Neurol. & Psychiat. **2**:45 (Jan.) 1939.

In his critical review of the value of therapeutic narcosis, Gillespie states that continuous narcosis if thoroughly carried out is still fraught with some danger, in spite of modifications in treatment. Freedom from risk is proportionate to the experience and care of those undertaking the treatment. The rate of recovery with continuous narcosis in cases of recent psychoses never exceeds, and usually falls short of, the rate of ultimate spontaneous recovery. Its therapeutic value is therefore confined mainly to curtailing the duration of psychotic conditions which would eventually pass spontaneously. It is most successful with manic excitements

and considerably less successful with depressions of the manic-depressive type. In the treatment of recent schizophrenic disorders its effects are best in cases of excited schizophrenia of the agitated fearful type and of hebephrenia in which the onset has been acute. Psychogenic schizophrenic disturbances in schizoid psychopathic patients are particularly amenable to this method. Little success is obtained with paranoid schizophrenia and with catatonic stupor. In general, when a psychotic illness follows a relapsing, recurring or periodic course, with an acute onset and exogenic causes, continuous narcosis is more likely to curtail the episode. These are essentially the more spontaneously recoverable types. Continuous narcosis also has an administrative value in making chronic psychotic excitements more manageable. Occasional unexpected social recoveries are produced in cases of chronic depressive (affective) psychoses and chronic schizophrenia. Recently, two authors obtained an unprecedentedly high rate of recovery and discharge in a small group of schizophrenic patients in whom the duration of the illness was more than two years. The treatment is still entirely empiric, and its efficacy is difficult to estimate because different investigators employ varying diagnostic criteria.

J. A. M. A.

Surgical Treatment of Pain. Julian Taylor, Lancet **2**:1151 (Nov. 19) 1938.

In pain due to involvement of nerve axons little can be expected from surgical measures, whereas pain brought about by pressure on a nerve by some external process can be readily eliminated. This principle of Wilfred Trotter is substantiated by three types of cases which are described by Taylor: painful fingers, painful stumps and ruptured intervertebral disks. Pain in the fingers may result from cicatricial involvement of a cutaneous digital nerve or, more rarely, from "infective neuritis." In only 1 of 3 cases was relief obtained by excision of a minute neuroma. Section of a digital nerve in another case aggravated the pain. Complete relief from pain was obtained by contralateral chordotomy in 7 cases in which pain was due to neoplasm of the femur, amputation neuromas or an eroding aneurysm of the aorta. In a case of "hernia of the nucleus pulposus" complete relief from pain was achieved by excision of the bulging disk and adjoining articular cartilage. The pain in such cases is due to pressure on the fifth lumbar root, which becomes wedged between the protruding disk and the pedicle of the lumbar vertebra. This accounts for the pain in the dorsum of the foot and over the heel. Operation should not be done in such cases, and iodized poppy seed oil should not be injected unless physical therapy and other measures have proved fruitless. Injection of procaine hydrochloride should be tried before alcohol is injected in instances in which an organic cause is suspected but not verified.

Krinsky, Boston.

Grave Postoperative Attack of Paroxysmal Tachycardia Treated Successfully by Procainization of Left Stellate Ganglion. R. Leibovici, L. Dinkin and Wester, Presse méd. **47**:83 (Jan. 18) 1939.

Leibovici and his associates report the clinical history of a man aged 29 in whom there developed a severe form of paroxysmal tachycardia after appendectomy. Since energetic medication was without effect on the tachycardia, it was decided to arrest the tachycardia by injecting procaine hydrochloride into the left stellate ganglion. About 20 cc. of a 1:200 solution of procaine hydrochloride was injected slowly. The effect was immediate. The pulse rate fell suddenly from 180 to 72, and the patient felt greatly relieved. In the minutes which followed the injection, Bernard-Horner's syndrome developed and persisted for several hours. This confirmed that blockage of the stellate ganglion had been accomplished. The pulse rate remained normal (about 76 to 80). The course was uneventful, and the patient was discharged on the eighth day. Four weeks after the intervention examination of the heart revealed nothing abnormal. The patient

did not have another attack of tachycardia. The authors cite factors which indicate that the case was one of paroxysmal rather than of sinus tachycardia, and then point out that it is no longer disputed that the sympathetic system plays a part in sinus tachycardia and that surgical interventions on this system have been employed with success in a number of cases of sinus tachycardia.

J. A. M. A.

CONVULSIVE THERAPY BY MEANS OF ELECTRIC SHOCK. V. CERLETTI and L. BINI, Arch. gen. di neurol., psichiat. e psichoanal. **19**:266, 1938.

Cerletti in 1934 employed an alternating current of 125 volts to produce experimental convulsions in dogs. After the introduction of the treatment of schizophrenia with convulsants, the method was modified for use with human beings. The apparatus consists of a timer, capable of regulating the length of a shock over fractions of a second, and a means of measuring and graduating the current. A supplementary apparatus measures the resistance of the subject's head by means of a minute current. The electrodes are applied by means of a special band. A current of 300 to 600 milliamperes at a strength of 8 to 115 volts, applied for five to seven-tenths second, is ordinarily used. When the current is applied, the patient immediately loses consciousness without sign of distress, and there develops a generalized tonic spasm. This is followed by pallor and then cyanosis; the respiration is arrested for a moment. After about thirty seconds the color returns, and a typical generalized convulsion occurs, lasting about two minutes. The pulse rate is little affected. Consciousness is regained in eight to ten minutes, and the patient has no memory of what has occurred. The excitement sometimes produced by metrazol is lacking. The attack may be repeated immediately if desired. The method has not yet been used in a sufficient number of cases to justify an opinion as to its therapeutic value. The results so far have been good, and there is every reason to believe that they should at least equal those produced with other convulsants, with less danger.

PUTNAM, Boston.

REEXAMINATION OF PATIENTS TREATED FOR DEMENTIA PARALYTICA WITH MALARIA. F. ESCHER, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:37, 1938.

Four hundred and thirteen patients suffering from dementia paralytica were admitted to the Burghölzli Hospital, Zürich, between 1922 and 1934. As only 58 of these entered the institution voluntarily and most of the remainder presented a well developed psychosis on admission, the material was regarded as unfavorable from the standpoint of treatment. Dementia was indeed so far advanced in 22 cases as to render treatment inadvisable. It was formerly considered desirable to permit patients inoculated with malaria to have twelve chills, but in later years the number was reduced to eight. Fever therapy was generally followed by a course of treatment with arsphenamine and bismuth.

At least two and one-half years had elapsed since treatment in every case, the interval being three years or longer in the majority. Three hundred and ten patients had been treated with malaria, but only 296 could be reexamined. Of the latter group, 134, or 45.2 per cent, had died; 16, or 5.4 per cent, showed complete remission, and 55, or 18.9 per cent, had partial remission; 26, or 8.8 per cent, were somewhat improved (remission of the third and lowest grade), and 58, or 19.6 per cent, were unimproved. The result of treatment was unknown in 7 cases, or 2.1 per cent. In confirmation of the general impression relative to the high mortality in patients not responding to treatment, it was found that four fifths of those who died were in fact unimproved. In 10.3 per cent of the 155 patients still alive at the end of 1937, the condition was in complete remission, and in 35.5 per cent, in partial remission; 16.8 per cent of the patients were somewhat improved, and 37.4 per cent were unimproved.

The duration of the disease was more than one year in 146, or 55.6 per cent, of 261 cases in which the time of onset could be determined. Although, in general, the percentage of good results varied inversely with the time elapsed since the first appearance of mental symptoms, complete remissions were obtained in 2 cases of more than three years' standing. The element of time appeared to be more important than the clinical type of the disease, though remissions were most frequent in euphoric and depressed patients and least frequent in agitated patients.

Cerebrospinal fluid was obtained from 97 of the 155 patients who were still alive. The complete formula for dementia paralytica was obtained with the fluid of only 6 patients; these were patients treated between 1930 and 1934, as were all the 20 persons whose fluid gave positive Wassermann or flocculation reactions. So far as mortality was concerned, return of the spinal fluid to a normal state seemed to be the most favorable prognostic sign. Lack of any close correlation between clinical improvement and reversal of the spinal fluid reactions was attributed to the fact that most of the patients received treatment relatively late. Positive Wassermann or flocculation reactions of the blood were found in more than a third of the patients having normal reactions of the cerebrospinal fluid, but little significance was attached to this. Wassermann or flocculation reactions of the blood were positive in 16 of the 20 cases in which there were similar reactions of the spinal fluid.

Three cases are reported in which dementia paralytica became manifest clinically soon after injury to the head. In spite of prompt treatment with malaria, the result was unsatisfactory in all 3 cases, the patients being in a demented state when examined from four to five years later. Since it appeared that trauma had served merely to hasten the appearance of symptoms, only six months' compensation was awarded in each case. The author expresses the view that experience in a large number of cases would be needed to confirm his impression relative to the unfavorable response of dementia paralytica to treatment when aggravated by cerebral trauma.

Details in 2 cases are given in support of the author's contention that if there is such a condition as "fluid-negative dementia paralytica," such a diagnosis should be made only after careful study. The diagnosis of dementia paralytica, originally made on purely clinical grounds, was in both instances subsequently proved to be wrong.

DANIELS, Denver.

NORMAL HUMAN SERUM IN THE TREATMENT OF MULTIPLE SCLEROSIS. E. STRANSKY, Monatschr. f. Psychiat. u. Neurol. **98**:237 (June-July) 1938.

Starting with the idea that multiple sclerosis is caused by an unknown infectious agent, Stransky assumes that persons who remain free from the disorder possess immune bodies in the blood. Therefore he attempted to determine whether beneficial results can be produced by administering normal blood serum to patients with multiple sclerosis. Since the disease usually affects young adults, rarely beginning after the age of 50, the serum was obtained from healthy persons whose ages exceeded that limit. Twenty patients with multiple sclerosis were given subcutaneous or intramuscular injections of serum in doses of from 10 to 20 cc. daily or every other day, the total amount ranging from 50 to 300 cc. Five patients showed pronounced and rapid improvement, which has been well maintained, though the longest period of observation in any case was eight months. Twelve patients displayed less marked or transient improvement. While Stransky is aware of the pitfalls in evaluating therapeutic procedures in such a changeable condition as multiple sclerosis, he does not believe that the striking results noted by him can be due to spontaneous remissions. In his opinion, the disease is favorably influenced by treatment with normal human serum.

ROTHSCHILD, Foxborough, Mass.

Special Senses

OPTOCHIASMIC ARACHNOIDITIS. DERRICK VAIL, Arch. Ophth. **20**:384 (Sept.) 1938.

Vail's conclusions are based on a survey of 134 cases in which the diagnosis of optochiasmic arachnoiditis was verified by operation. The disease occurs in young adults, over 80 per cent of the cases occurring in persons under 40. The condition predominates slightly in the male. Vision in one eye is usually affected long before the second eye is involved, and loss of vision is likely to be rapid. The earliest symptoms are those of acute retrobulbar optic neuritis, with almost always a central or cecocentral scotoma in the field of vision. Bitemporal, binasal or homonymous hemianopias are frequently associated with the scotoma. Several combinations of signs may occur, as outlined by Craig and Lillie: (1) unilateral central scotoma with normal fundi; (2) unilateral central scotoma and pallor of the disk but normal conditions in the other eye; (3) bilateral central scotoma with pallor of both disks; (4) bilateral central scotoma with choked disks; (5) unilateral amaurosis with simple atrophy of the optic nerve and choked disk in the opposite eye, sometimes associated with a central scotoma; (6) central scotoma and various alterations of the peripheral fields due to secondary contraction resulting from choked disks, and (7) bilateral amaurosis with any of the foregoing changes in the fundus.

The appearance of the optic nerve, which seems to lie between the primary and the secondary type of atrophy, is suggestive of arachnoiditis involving the chiasm. Vail was struck by the number of cases in which the outline of the disk was sharply defined and the lamina cribrosa was visible but the caliber of the vessels was markedly reduced. He confirms the findings of Bollack, David and Puech that in 38 per cent of instances there is papillary atrophy of the primary type. In 15 per cent the atrophy is accompanied by blurred margins of the disks; in 10 per cent there is partial atrophy, and in 7 per cent there is simple hyperemia. Disks with horizontal atrophy appeared in 4 per cent of the cases, and in 18 per cent the disks were either normal or difficult of interpretation.

Vail found frequent remission of visual loss in the course of the disease. It seemed as if the ocular symptoms improved momentarily, only to be followed by a new attack and further loss of vision. The roentgenograms in general were normal. In a few cases calcified areas were observed, leading to an erroneous diagnosis of tumor of Rathke's pouch.

Vail concludes that optochiasmic arachnoiditis is a clinical entity, presenting certain signs and symptoms which on careful study may lead to a proper preoperative diagnosis. At any rate, the signs point to involvement of the chiasmal region and warrant surgical exploration, at which time the diagnosis can be made. Case reports indicate that surgical intervention is justified on the basis of the improvement in vision which follows in most cases.

The posterior nasal sinuses may be the portal of entry for the toxin or virus, and recent evidence indicates that encephalitis, multiple sclerosis and the associated demyelination diseases, as well as optochiasmic arachnoiditis, may all be closely allied and may be different manifestations of the same pathogenic process. The many cases of retrobulbar optic neuritis in which dramatic improvement of vision occurs after treatment of the sinuses, whether by surgical or medical procedures, justify sinus treatment. It is too soon to say that signs of multiple sclerosis will not develop later in cases of optochiasmic arachnoiditis.

SPAETH, Philadelphia.

HOMONYMOUS HEMIANOPIC PARACENTRAL SCOTOMA. T. D. ALLEN and H. F. CARMAN JR., Arch. Ophth. **20**:846 (Nov.) 1938.

Allen and Carman report a case of homonymous hemianopic paracentral scotoma occurring in a woman aged 48, who showed no other neurologic signs. The fundi were normal; there were no pathologic changes of the retinal vessels.

The defects which were elicited had decreased decidedly ten months after the first examination. The authors believe that the lesion was probably at the level of the lateral geniculate bodies.

SPAETH, Philadelphia.

ANGIOMATOSIS RETINAE. ROBB MCDONALD and STUART W. LIPPINCOTT, Arch. Ophth. **20**:958 (Dec.) 1938.

The authors report a case of angiomatosis retinae, with a pathologic study of the enucleated eye. A boy aged 15 was first seen because of loss of vision in the right eye. There seemed to be a connection between the condition and a trauma several years before. Microscopically the disk could not be seen, but just above the posterior pole an enormously dilated vein was visible in the upper temporal quadrant. It coursed in a serpentine fashion over the many folds of the detached retina, the forward displacement of which increased temporally and below. The vein ended abruptly in a large reddish cyst in the extreme periphery, about 1 disk diameter above the horizontal meridian. It was followed above by a similar dilated vessel of slightly smaller size; it was hidden in part of its course by the many folds of the retina, but it could be seen to enter the cyst just above the vein. There were two other cystlike dilatations. The vessels, especially those communicating with the cysts, were enormously dilated and tortuous and had a peculiar reddish reflex, which gave the impression that they were about to burst. The entire temporal and lower half of the retina was detached, the detachment being uneven, with many undulating folds. Its color varied from red to yellow; in places it was of a greenish hue. No normal area was seen in the fundus. A small sector of retina above appeared to be attached with normal vessels, but the retina was yellow and atrophic.

SPAETH, Philadelphia.

LESION OF THE OPTIC TRACT. ALBERT N. LEMOINE, Arch. Ophth. **20**:966 (Dec.) 1938.

Lemoine reports a case of a lesion similar to retrobulbar neuritis, but which lay behind the chiasm. The findings and the course of the disease suggest that disease of the sphenoid sinus was the cause. The patient's impairment of vision developed abruptly and progressed gradually until vision in the right eye was limited to counting fingers at 1 foot (30 cm.) and in the left eye was about 20/60. The fields of vision showed first a left inferior homonymous defect involving the macula; thirteen days after operation on the sphenoid sinuses there was concentric contraction for all colors. The only positive findings were a mucocele within the right antrum and an abnormal sphenoid sinus. There was also a marked general increase in the intranasal tissue, with the turbinate bones apparently much hypertrophied and thickening and mild deviation of the nasal septum to the right.

The roentgenographic picture showed a significant pathologic process within the sphenoid sinuses. As a result of this, submucous resection was performed, with radical operations on both the sphenoid and the ethmoid sinus. Operation revealed thickening of the mucoperiosteal lining of both sphenoid sinuses, with a hemorrhage into the mucoperiosteal lining of the posterior superior wall of the right sphenoid sinus. There was no pus in either sinus on the day after the operation. Vision improved, and on the second postoperative day the patient could read large print. Thirteen days later visual acuity was 20/200 in the right eye and 20/20 in the left eye. Two months later vision was 20/20 in each eye.

The author concludes: "I feel that all patients with retrobulbar neuritis should be thoroughly studied, especially those in whom the condition seems to be secondary to disease of the posterior nasal sinuses. Such studies may lead to the solution of the perplexing problems of the underlying causes of multiple sclerosis and other demyelinating diseases."

SPAETH, Philadelphia.

RELAPSING OPHTHALMOPLEGIA. G. DE MORSIER, Rev. d'oto-neuro-opht. **17**:350 (Jan.) 1939.

The pathologic nature of relapsing ophthalmoplegia is unknown. De Morsier reports observations in 2 cases in which the initial episode sheds new light on the nature of the disease. In both the malady was inaugurated by encephalitis. The conditions in the 2 cases fit well into the picture of the disease described by Bielschowsky, except that the first patient suffered from violent headaches. The absence of pupillary disturbances is emphasized, as well as the alternating character of the paralysis and the regular periodicity of eight years between attacks in the first case. The inflammatory origin of the syndrome appears certain, but the cause of the periodicity and the remissions is not known.

DENNIS, San Diego, Calif.

CONNECTIONS OF THE SUPERIOR COLLICULI WITH OTHER OPTIC PATHWAYS AND CENTERS. ADOLF JUBA, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:273 (Jan.) 1939.

Juba reports 2 cases, in which some of the central connections of the superior colliculi are illustrated. The first case was that of a woman aged 58 who had an enucleation of the left eye and died about two months later. At autopsy, syphilitic aortitis, pulmonary emphysema and bronchopneumonia were observed. An old area of softening was present in the left occipital cortex. The relatively recent enucleation of the eye and atrophy of the left optic nerve made it possible to study the relation of these changes to alterations in the superior colliculi. In the right superior colliculus there was evidence of marked degeneration with the Marchi stain. The stratum medullare superficiale was particularly involved. These changes prove that there exists a definite connection between the optic nerves and the superior colliculi. Balado and Franke recently denied that any such connection has been adequately demonstrated in man.

The second case was that of a woman aged 62 who was admitted with a history of dizziness for three weeks and marked diminution of vision for three days. Examination revealed arterial hypertension, bilateral cataracts, hyperactive knee and ankle jerks on the right side and a positive Babinski sign on the right. The patient died seven days after admission. Autopsy revealed multiple areas of softening in the brain and thrombosis of the basilar artery. There were bilateral softenings in the striate areas. The internal sagittal strata were involved on both sides, more extensively on the right. There were degenerative changes in both superior colliculi more extensive than in the first case and involving the superficial medullary strata. The degeneration was observed in the first two layers of the colliculi. There was no difference between the two sides, in spite of the definite difference in extent of involvement of the internal sagittal strata. The changes in the superior colliculi can therefore be correlated only with the softenings on the medial surface of both occipital lobes. This case proves the existence of efferent connections between the striate region of the occipital lobes and the superior colliculi. The opticomotor fibers therefore probably have origin on the medial surface of the occipital lobes. In the first case the absence of older changes in the superior colliculus secondary to the lesion in the occipital lobe may be explained by the fact that in this case the more anterior part of the calcarine area was involved. Most of the opticomotor fibers probably arise from the posterior part of this region.

SAVITSKY, New York.

PAPILLEDEMA AND HYPERTENSION. I. AASLAND, Norsk mag. f. lægevidensk. **1**: 108 (Jan. 14) 1939.

Aasland says that while the origin of the various disorders in which choked disk may appear differs, the common factor in all is arterial hypertension. He thinks that the extreme form with intracranial pseudotumor occurs only in cases of malignant hypertension. The picture of pseudotumor depends on arterial hyper-

tension in the cranial blood vessels with secondary symptoms of circulatory insufficiency in the form of general edema and increased intracranial pressure. The increased pressure of the cerebrospinal fluid, which is often present in malignant hypertension, is assumed to be an accessory factor in the mechanism of choked disk. Two cases of intracranial pseudotumor associated with malignant hypertension are reported. There were bilateral papilledema of 5 and about 7 D., respectively. The blood pressure varied from 230 to 250 mm. of mercury. In the second case the pressure of the cerebrospinal fluid rose to 360 mm. No signs of renal disease were established in either case. Necropsy revealed no evidence of cranial tumor. In spite of recommended treatment, such as intravenous administration of hypertonic solutions, repeated lumbar puncture and depressive craniotomy, the prognosis is grave. According to statistics, in 90 per cent of the cases the disease is fatal within two years after the beginning of the hypertensive changes in the eyeground, and in most of the remaining 10 per cent within the next two years.

J. A. M. A.

Diagnostic Methods

THE DETERMINATION OF SPINAL FLUID PROTEIN WITH THE PHOTOELECTRIC COLORIMETER. J. M. LOONEY and ANNA I. WALSH, J. Biol. Chem. **127**:117, 1939.

A method for the determination of spinal fluid protein with the photoelectric colorimeter is described. The precipitation of protein by sulfosalicylic acid was made in the presence of ghatti gum and yielded a stable colloidal suspension, which did not change for thirty hours. Concentrations of proteins of from 5 to 150 mg. per hundred cubic centimeters can be read without dilution.

PAGE, Indianapolis.

UNEQUAL NARES AS A NEW DIAGNOSTIC AID. JOSHUA H. LEINER, J. Nerv. & Ment. Dis. **88**:771 (Dec.) 1938.

Leiner notes that in supranuclear, nuclear or infranuclear paralyses of one side of the face the anterior naris is flattened, or even collapsed, on the affected side. Complete collapse is found with involvement of the nucleus and peripheral nerve. The sign is of value in comatose patients. It is absent in cases of hysterical paralysis.

MACKAY, Chicago.

RESONANCE OF THE SKULL IN RELATION TO THE STATE OF THE LABYRINTH. T. DEMETRIADES, Rev. d'oto-neuro-opht. **16**:608 (Nov.) 1938.

At various times, while examining patients with intracranial tumors, Demetriades noticed that in the majority increased cranial resonance coincided with the side of the tumor and of the most marked labyrinthine lesion. Experiments demonstrated that the blood vessels of the cranium played an important role in cranial resonance, the latter being increased on the more hyperemic side. The resonance was measured by placing a band to which were attached two auscultation tubes, around the forehead and the two mastoid regions, setting a vibrating tuning fork on the forehead and comparing the resonance of the two sides of the head through the auscultation tubes. The resonance of the right side was normally greater than that of the left, supposedly because of the greater tonus of the right labyrinth. Other experiments showed that the labyrinth (vestibular nerve) influenced the vascular equilibrium, and hence the resonance, of the head. Stimulation of the labyrinth caused contraction of the vessels and reduction of the resonance of the side to which the nystagmus was directed. On the other hand, a lesion of a labyrinth caused a decrease of the resonance on the corresponding side of the head. Hence, the strongest resonance was found on the side of the most irritable labyrinth, the brain and the rest of the head being normal. If, now, encephalic hyperemia was produced, sufficient to overcome the anemia caused by the labyrinthine lesion, the following syndrome appeared: increased resonance on the

side of the more feeble labyrinth. Examination in 27 cases of cerebral tumor revealed that the syndrome was present in 22. It is important to use Kobrak's caloric method, modified by Demetriades, in order to discover the finer shades of labyrinthine excitability. The phenomenon occurred in all cases of extensive hyperemia of the head, provided the latter or its cause produced a labyrinthine lesion. Such hyperemia accompanies cerebral tumors especially. Disease of the accessory nasal sinuses, malignant tumors of the epipharynx, otitis media and acute mastoiditis may influence cranial resonance. DENNIS, San Diego, Calif.

AN OPHTHALMOSCOPIC SIGN OF INTRACRANIAL HYPERTENSION. J. R. KAEFER, Rev. neurol. de Buenos Aires **2**:443, 1938.

Normally, compression of the jugular veins produces a definite change in the appearance of the veins of the fundus, as seen by the ophthalmoscope: The caliber increases; the color becomes lighter; if there are venous pulsations they decrease and disappear. When pressure on the jugular vein is released, the phenomena reappear in reverse order.

As the existence of papilledema appears to be dependent, at least in part, on increase of venous pressure, it seems reasonable to suppose that the elasticity of the veins may be taken up by the existent pressure. Kaefer proposes, therefore, as a sign of increased intracranial pressure the diminution or disappearance of the alterations normally produced in the central retinal vein and its tributaries by compression and release of the jugular veins. The compression should be carried out by an assistant, gradually, but with a sudden release. The sign should be more delicate than that of Bailliart, since the walls of the veins are thinner. The author presents a preliminary report of the use of the test in 15 cases, in all of which it appeared to be successful. In a patient with an operative decompression the sign could be demonstrated when the decompression was full or was pressed on, but not when it was loose. PUTNAM, Boston.

MASTIC REACTION IN CASES OF ACUTE ANTERIOR POLIOMYELITIS. K. G. KAIJSER, Acta med. Scandinav. **98**:209 (Jan. 12) 1939.

Kaijser says that little attention has been given to the mastic reaction in cases of acute anterior poliomyelitis. Nevertheless, several observers have shown that a type of mastic reaction can be evolved which is characteristic for poliomyelitis. The mastic test has been employed in cases of experimental poliomyelitis in monkeys as well as for the early diagnosis of poliomyelitis in human subjects. Kaijser studied the value of the test first in 14 cases of acute anterior poliomyelitis accompanied by paralysis. He reports the clinical histories in these cases and the outcome of the mastic test. It was found that in certain cases of poliomyelitis in which paralysis exists at the time of the examination of the cerebrospinal fluid there is a typical mastic reaction. In the majority of these cases only moderate flocculation was observed in the tube that contains the strongest concentration, and the maximum of flocculation appeared in the second, third and fourth tubes. In the succeeding tubes it subsided; it usually disappeared completely in the sixth or seventh tube. The average curve of the mastic reaction in these cases is represented by the figures 123321000. Having determined that in poliomyelitis with paralysis there is a typical curve, the author studied the mastic reaction in cases of two other types of disorders, namely, in 10 cases of acute anterior poliomyelitis without paralysis and in 5 cases in which poliomyelitis was suspected. In the 10 cases of abortive poliomyelitis the curve of the mastic reaction was not as uniform or as characteristic as in the cases of poliomyelitis that was accompanied by paralysis. In the cases of the abortive type the maximum flocculation was usually observed in tubes 2, 3 and 4. In the 5 cases in which poliomyelitis was only suspected, the mastic reaction was similar to that under normal conditions. The impression was gained that in these 5 cases there existed a disorder other than poliomyelitis. J. A. M. A.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

BALDWIN L. KEYES, M.D., *President, in the Chair*

Regular Meeting, March 10, 1939

A CASE OF CHANGE IN PERSONALITY FOLLOWING TYPHOID FEVER. DRS. ORVILLE HORWITZ (by invitation) and HAROLD D. PALMER.

A change in personality occurred in a young man as the result of a serious, prolonged and depleting illness (typhoid). The report has special value at this time, when new and potent forces for the production of personality changes in psychotic patients are receiving widespread attention. The patient, then in the medical service of Dr. D. L. Farley, at the Pennsylvania Hospital, was seen in psychiatric consultation in December 1938. The fundamental alteration in personality and temperament observed paralleled certain objective changes in the endocrine status. The data given by the patient were verified by an aunt, who was a graduate nurse and a thoroughly reliable observer. The patient was highly intelligent and was able to evaluate the changes with unusual insight and validity. The three phases of his illness covered a space of eight years and were all studied in the wards of the Pennsylvania Hospital. Accurate records are available. The patient had excellent rapport with the physician, and a thoroughly confidential relationship was established. Therefore, the chances of any purposeful or accidental inaccuracies were reduced to a minimum.

The patient was first admitted to the Pennsylvania Hospital on July 19, 1931, when he was 14 years of age, the diagnosis being rheumatic heart disease with mitral insufficiency, questionable mitral stenosis and adhesive pericarditis. The patient was discharged on July 29, 1931. He was advised to lead a restricted life, which he did for about six months. After that he gave his cardiac condition little thought. His second admission was on Aug. 30, 1936, when he was 18 years of age. In the interval he had graduated from high school at the head of his class; he was athletic and physically strong and played semiprofessional baseball. It was stated that during these years he was "on the go" all the time and was obviously extrovertive. He was employed as a clerk, but continued his athletic interests after working hours. Sexually he could be considered as slightly precocious, in that heterosexual relations were established at about 17 years of age and were continued. He also indulged in masturbation several times a week. His aunt described him as a strong and stockily built, masculine person, unusually intelligent, with good powers of concentration and memory. He was a good mixer. The patient described himself as "a little wild," but there was nothing to indicate that he was abnormally so. The members of his family were mostly of pyknic habitus, tending toward obesity. Two brothers and two sisters were in good health. His second hospitalization, lasting ten weeks, was occasioned by a severe attack of typhoid. His temperature remained between 102 and 104 F. for the forty days, without remission. Cultures of the stool, urine and blood all yielded Bacillus typhosus. The Widal reaction was strongly positive. The patient's weight dropped from 205 to 150 pounds (93 to 68 Kg.). There was one relapse. After recovery from this illness, now nearly three years ago, his life was entirely different. He lacked ambition; his former drive and energy seemed to be absent; he did not indulge in any form of athletic activity, and his sexual life was curtailed. He continued to work regularly from 3 p. m. until midnight in a clerical position. During this time there developed a number of phobias and

obsessions, particularly related to the bookkeeping. He had a compulsion to check and recheck his figures, although he knew that his books were in good order. He could not resist the urge to go over and over them, "just to be certain." He became increasingly religious and attributed part of his loss of sexual desire to his preoccupation with religious matters. He began to read a great deal of psychology and became rather morbid, tending to concentrate on freudian literature.

Relatives stated that after the attack of typhoid the patient showed many effeminate traits, and during his recent stay in the hospital (Dec. 1 to 27, 1938) the ward nurses and other patients frequently commented on his effeminate gestures and mannerisms. During the interview, though speaking frankly, he showed embarrassment and displayed many girlish gestures. He stated that he was depressed because he believed that he had brought on some of his difficulties through masturbation. He felt that there was no one at home with whom he can talk about his worries, and friction had developed in the household, particularly in his contacts with his mother. He was worried about the lack of physical energy and felt at times that life was not worth living. He said: "I feel as if I am going to lose control of myself, or that I am going goofy." He had impulses to scream and to break things, and said that at times it was all he could do to refrain from knocking a pitcher or glass to the floor or throwing something through the windowpane. He had become definitely introverted and felt that people could see certain traits which were unfavorable by simply looking him in the eye. He could no longer look directly at people. He observed that he had developed a feminine type of body contour and that his genitalia had decreased in size. Interest in sex matters had declined remarkably.

Physical Examination.—The patient, aged 21, was obese and had feminine distribution of hair and a soft, pink skin. His weight was 217 pounds (98.4 Kg.) and his height 5 feet 8 inches (172.7 cm.). There was an abnormal deposit of fat about the buttocks, hips, breasts and thighs. The genitalia were slightly smaller than normal, and his beard was not thick or coarse, but downy. He said that the facial hair had changed decidedly from that which was present at the age of 18. The heart seemed to be in good condition; there was no definite enlargement; there were a rough systolic first sound at the apex and a systolic murmur in the pulmonary area. The blood pressure was 120 systolic and 70 diastolic.

Laboratory Studies.—The basal metabolic rates were 1 plus, 8 plus and 2 plus on December 3, 13 and 30, respectively. Roentgenograms of the chest revealed no abnormality of the thymus gland and no evidence of cardiac enlargement; the pulmonary fields were clear. A roentgenogram of the skull revealed a normal pituitary fossa. An electrocardiogram showed inversion of all waves in lead III, which is frequent with a high diaphragm, as in obesity. Blood studies gave normal results except for slight plethora of the red cells. The Wassermann reaction was negative. Urinalyses gave normal results. Examination of the stools did not show typhoid, paratyphoid or dysentery bacilli. The visual fields were normal; the patient was slightly myopic, Dextrose tolerance tests, with ingestion of 100 Gm. of dextrose, gave the following results:

Dec. 12, 1938	Gm.	Dec. 19, 1938	Gm.
Fasting	0.086	Fasting	0.078
1 hr.	0.110	1 hr.	0.092
2 hr.	0.084	2 hr.	0.075
3 hr.	0.095	3 hr.	0.077
4 hr.	0.060	4 hr.	0.064
		5 hr.	0.072
		6 hr.	0.075

Summary.—Before the attack of typhoid the patient was active, outgoing, socially well adjusted, ambitious, happy and completely extroverted, with labile mood. There was an abundance of masculine sex drive, and he was muscular, energetic in athletics and typically pyknic. From the physiologic point of view he was definitely masculine, with excessively heavy body hair and beard and normal genitalia. He displayed masculine behavior and mannerisms. After the

severe attack of typhoid, in 1936, he became lazy and inert and showed withdrawing, passive, introverted behavior with hypochondriacal trends. He was unhappy and depressed, had no athletic activities and showed many obsessive-compulsive trends, with the development of religious and pseudopsychologic preoccupations. He presented feminine traits and mannerisms and feminine body contour, with female distribution of hair. There were a decrease of libido and a flat emotional tone.

This case is thought worthy of consideration in view of the enthusiasm with which shock therapy has been received. Psychiatric vision may be somewhat obscured by the violence and magnitude of the physical reactions and the physiologic changes produced by shock treatments. There has not been time to evaluate fully all the psychic phenomena and the subtle changes that may occur in the personality. A few contributions to recent literature have indicated an attempt to think in psychiatric terms about the effects on the personality as a whole. Feldman, Fiero and Hunt (*Psychiatric Quart.* **12**:710 [Oct.] 1938) reported on the personality changes produced by insulin therapy in 3 schizophrenic patients of the paranoid type. All had shown definitely introverted prepsychotic personality traits, with gradual shading into schizophrenic reactions and, finally, outspoken schizophrenic psychoses. The course of the insulin treatment was short in all 3 cases, consisting in the first of 32 treatments, 12 of which produced comas, in the second of 24 treatments, in 19 of which there was coma, and in the third of 13 treatments, in 5 of which there was coma. None of the patients had convulsions. After treatment all displayed marked changes in personality, a shift from an introverted, asocial, withdrawing makeup to that of an extroverted, social and well balanced attitude. In 2 of the cases the improvement was of short duration. In 1 patient who relapsed the recurring psychosis was remarkable in that it appeared to be a hypomanic disorder, strong in contrast with the previous schizophrenic reaction. In the third case the sociable, extroverted, well balanced attitude continues after the end of one year.

There have recently appeared several articles dealing with a Korsakoff-like syndrome in schizophrenic patients following insulin and metrazol shock therapy. Dr. E. D. Bond, in reviewing the cases of patients at the Pennsylvania Hospital who have improved or recovered with insulin therapy, remarked on the apparent extroversion of the recovered patients. The patient whose case is reported showed an apparent reversal of such personality changes, that is, an alteration in personality from a normal, extroverted, outgoing athletic type to an introverted, effeminate, neurotic reaction type. Accompanying this change has been a physiologic one which can best be characterized as pituitary-gonadal insufficiency. From the standpoint of shock to the nervous system and to the endocrine glands, may not the severe typhoid, with forty days' exposure to high temperatures, be the equivalent of shock therapy? Unquestionably, psychiatrists have seen many patients who have shown similar changes in personality due to severe illness. In obtaining detailed medical and psychiatric histories, the general practitioner, internist and pediatrician encounter subtle changes in personality, which are often accepted without adequate thought of the relation of the presenting disturbance of personality to the agent or the precipitating physical illness.

DISCUSSION

DR. J. C. YASKIN: Is there any information regarding the patient's endocrine makeup prior to having typhoid?

DR. ORVILLE HORWITZ: No special endocrine studies were made prior to this illness, but a record of his physical state is available, since the patient was previously in the Pennsylvania Hospital and at that time nothing suggested glandular dysfunction.

DR. J. C. YASKIN: There can now be no question that this man had definite endocrine dysfunction and introverted traits. It would be interesting to learn how frequently such personality changes were noted after typhoid in the days when it was prevalent. It is known that encephalitis frequently accompanies typhoid.

DR. B. L. KEYES: A case of this sort suggests that there is need for exercising care in the use of violent shock therapy in cases in which a favorable outlook would otherwise be expected, if an organic illness can produce such distinct personality changes.

DR. HERBERT FREED: I am still of the opinion that shock therapy should be given as soon as a diagnosis can be made, in spite of the fact that there may be some dangers, as suggested in this case. Indeed, it may not be important to wait for a positive diagnosis in view of present knowledge concerning the value of the treatment in manic-depressive conditions.

DR. HAROLD D. PALMER: The changes in fundamental personality type reported as a result of the shock therapies and the personality reversals due to febrile or toxic states, as illustrated by the case just reported, have certain deep implications. Personality types in relation to endocrine pattern and, further, in relation to the fundamental psychobiologic affinities (as formulated by Kretschmer) have been thought to be fixed constitutional imprints. If, in recent experience with insulin therapy and in a more careful observation and study of changes produced by illness one is really seeing fundamental changes in, or disruption of, the personality-body constitution affinity, a realinement of psychobiologic concepts is needed. This realinement, or reevaluation, must result in a less static, more physiologic or dynamic, concept. It must be flexible enough to allow for reversals (either in the direction of recovery or regression) if the physiologic readjustments induced by insulin and metrazol, or accidentally, as in the case reported, are of sufficient depth.

PSYCHOSIS DUE TO EPHEDRINE: REPORT OF A CASE. DR. HAROLD D. PALMER.

The toxic effects of ephedrine have been reported with remarkable infrequency in the literature. Only one report of nervous and mental toxic reactions has appeared in the past ten years. Higgins (Chronic Ephedrine Poisoning, *J. A. M. A.* **92:**313 [Jan. 26] 1929) described the case of a patient aged 36, whose condition had previously been diagnosed as hyperthyroidism. The patient had been given ephedrine sulfate, ½ grain (0.032 Gm.) in capsule form, three times a day after each meal, for the relief of asthma during a period of about four months. After about four weeks of administration of this dose she became nervous and tense, felt overtired and was unable to relax. Gradually there developed tremors, severe insomnia, nausea, shortness of breath, palpitation and jerking, choreiform movements. There was much crying, together with other evidences of emotional instability. Dr. Grier Miller (The Clinical Value of Ephedrine, *Am. J. M. Sc.* **170:** 157-181, 1925) reported nervous and psychologic effects, but they do not seem to be of great significance.

The case I shall report here is that of a professional man aged 44, who had for many years suffered from asthma and other allergic phenomena. In the summer of 1936 he began to take capsules of ephedrine sulfate (⅜ grain [0.024 Gm.]) two or three times a day and as often as from three to five times each night for the relief of severe asthmatic paroxysms. After five or six weeks of this high dose he became very nervous and "jittery," had frequency and urgency of urination and began to experience nervous tension and anxiety. He was sent to a resort hotel, where he underwent an acute hallucinosis of flighty character, heard accusing voices in an adjoining room and reacted by the development of great anxiety and fear. He expressed the delusion that he was being "framed" and persecuted, and he heard the hallucinatory voices plotting a "frame-up." He became so agitated that it was necessary to remove him from the hotel to a sanatorium, where he became acutely psychotic and had to be restrained. Here he expressed the delusion that he was being persecuted by the physician and nurses, and that he was to be castrated and tortured in many other ways. During his stay at the sanatorium he was allowed to continue the regular dose of ephedrine, amounting to approximately 6 capsules, ⅜ grain, of the drug per day. He also was given large

doses of sedatives, continuous tub baths and sedative packs to control his excitement and agitation. After two weeks in the sanatorium he was removed to the Pennsylvania Hospital, where he manifested the same flighty, apprehensive state and experienced auditory hallucinations of a character similar to those described. The ephedrine was withdrawn, and large doses of a sedative were given. Epinephrine hydrochloride, given hypodermically, was prescribed whenever needed to relieve the asthmatic paroxysms. The patient agreed to try to believe that the bizarre experiences were due to the ephedrine, but stated that he still felt convinced that he was not safe in the hospital or anywhere else. The other disturbances were nocturia, severe headache of dull general character, tachycardia, the rate varying from 100 to 120, increased respiratory rate and sweating of the hands and feet. There were a fine, rapid tremor of the outstretched extremities and slight incoordination in walking. The basal metabolic rate, red and white blood cell counts, urine and blood sedimentation time were normal; the fasting blood sugar level was 110 mg. per hundred cubic centimeters.

Ten days after discontinuance of the ephedrine sulfate the patient had returned to a normal state of mind and gave a thoroughly satisfactory personal history. It was learned that the patient had always been over conscientious and devoted to his work and had never married because he felt he could not support a wife and family. The remainder of the personal data gave no evidence of instability, nor were there any implications of a significant psychopathologic condition. The duration of the psychotic episode was approximately one month. The patient made a complete recovery while at the hospital and was sent on a convalescent trip for a month. On his return to his regular occupation late in October 1936, his family physician and the patient reported that he was in better health than he had been for years. Since that time he has worked steadily in a rather exacting occupation and has had no return of mental symptoms. He has continued to require fairly frequent doses of epinephrine to relieve the attacks of asthma and urticaria and now uses a 1:100 solution of epinephrine hydrochloride as a nasal spray, which has entirely replaced the hypodermic administration. Follow-up letters in January 1939 indicated that he had remained well since his discharge from the hospital.

A number of years ago Dr. Appel and I studied the circulatory and glycemic reactions of psychotic patients and normal controls to intravenous administration of 30 mg. of ephedrine hydrochloride in aqueous solution. The relevant findings were as follows: The manic-depressive patients showed distinct differences from the schizophrenic patients and normal subjects in blood pressure and glycemic responses (*Am. J. Psychiat.* **27**:159-171 [Jan.] 1932). In addition to the fundamental differences in responsiveness to the drug, there were many interesting side effects of nervous and emotional nature. In some of the manic-depressive patients there were unmotivated tearfulness, extreme nervous tension, headache, feelings of apprehension, tremors of the extremities and twitching of the facial muscles. Two manic-depressive patients stated that they felt as if they were "flying to pieces," and both shed large tears. Both stated that their emotions were of apprehension and fear, but not of sadness, and that they could not hold back tears, although they felt that crying was inappropriate to their emotions at the moment. Several of the normal subjects responded similarly, and they reported that fear and apprehension were pronounced, but that the crying was not explainable.

It is believed that some formulation of the nervous and mental toxic reactions to ephedrine should be attempted. The prodromal stages are characterized by persistent insomnia, feelings of nervous tension, emotional instability, crying on slight provocation, motor restlessness, tremors, sweating, fear, apprehension and unwarranted anxiety, excessive fatigue, inability to relax, nausea, shortness of breath and tachycardia. The psychotic manifestations are characterized by a peculiar flighty hallucinosis, marked chiefly by auditory phenomena, with vague

fear, apprehension, motor excitement and paranoid delusions centering about threats to the patient. The psychiatric syndrome is not unlike that observed in cases of severe thyrotoxicosis or alcoholic hallucinosis. The neurologic and physical findings are tremors of the extremities, amounting at times to severe choreiform movements; hyperactive tendon reflexes; twitching of the facial muscles; rapid pulse; rise in blood pressure; dyspnea, and excessive sweating. Differential diagnosis from hyperthyroidism can be made from the absence of an increase in basal metabolic rate, of a long history of excessive hunger and severe loss of weight, of enlargement of the thyroid and of the ocular signs of hyperthyroidism and the appearance of the symptoms with administration of ephedrine.

Treatment by withdrawal of ephedrine and substitution of epinephrine, either hypodermically or by intranasal insufflation, sedation with phenobarbital or sodium amytal, general hydrotherapeutic measures (sedative baths and packs) and psychotherapy in the form of reassurance as to the origin of the difficulty (and assurance of favorable outcome if treatment is entered into cooperatively) can be reasonably relied on to produce improvement or recovery within from seven to ten days.

DISCUSSION

DR. K. E. APPEL: Some years ago Dr. Palmer and I gave ephedrine to a group of schizophrenic and manic-depressive patients and to normal persons as a control. We found that the psychotic patients reacted differently to the drug than did the normal subjects.

DR. R. A. MATTHEWS: Dr. Palmer's paper brings up interesting possibilities. Some time ago a case of psychosis precipitated by the use of benzedrine sulfate was reported before this society, and now Dr. Palmer reports a case of mental illness precipitated by ephedrine, but to date I have no knowledge of any case in which a psychosis was produced by the use of epinephrine. These three drugs are said to belong to the adrenergic series; yet one must consider that ephedrine and benzedrine probably have a central effect as well. Whether a psychosis can be precipitated by drugs belonging to the cholinergic group remains to be demonstrated. This report is interesting when one considers present knowledge of the effect of the emotions on the autonomic nervous system, since here the reverse may have taken place; i. e., a drug which affects the autonomic nervous system produced an emotional reaction.

DR. M. W. THORNER: Apropos of Dr. Matthews' discussion, one must consider the possibility that the effect of ephedrine is to be evaluated in the light of the basic personality, and may not be expected in a person who does not show prepsychotic tendencies. About three years ago I used pilocarpine in treatment for myasthenia gravis. It had to be abandoned because of the frequency of the psychotic or near psychotic reactions which it produced. In regard to benzedrine, it is probably not correct to state that it is an adrenergic drug, since there is considerable structural difference between this preparation and epinephrine. Cole Davis noted that with epinephrine a smaller dose of metrazol, and with ephedrine a larger dose, is required to produce a response.

DR. HAROLD D. PALMER: My conclusion is that the direct nervous effect produced by the ephedrine was the condition which originally set off the emotions of fear, apprehension or anxiety. The hallucinations and delusions suffered by any patient, whether due to drug poisoning, infection or toxemia, always have some relation to events in the personal history. Undoubtedly in this case they took origin from certain personality traits and experiences in the patient's life. This does not mean that there were present any psychopathologic tendencies, any more than a patient with delirium during typhoid may be said to be reacting in a specific way only because of deeply rooted psychopathologic traits. The fact is that the patient was a successful professional man, recognized by his associates as reliable, stable and respectable and altogether a good member of society. The psychosis

was superimposed, and after removal of the toxic agent the man returned to stable normality and has remained well for nearly three years. The chief interest in the case lies in the fact that the patient went through a prodromal stage of insomnia, nervous irritability, "jitteriness" and anxiety due directly to ephedrine. He then passed into a state of acute, flighty hallucinosis, which was also due to continuation and exaggeration of the ephedrine effect. From this record and the case cited by Higgins one seems to be justified in formulating certain conclusions about the nature of the nervous and psychic reactions to ephedrine and certain helpful suggestions as to treatment.

PSYCHOSES PRECIPITATED BY SULFANILAMIDE: REPORT OF TWO CASES. DRS. MANUEL M. PEARSON (by invitation) and M. DAVID BURNSTINE (by invitation).

Two cases reported in the literature were reviewed, and 2 original cases observed at the Philadelphia General Hospital were presented.

CASE 1.—A sailor received sulfanilamide for gonorrheal urethritis. He presented a picture of confusion, bewilderment, disorientation and a mild paranoid trend. The psychosis completely disappeared in four days, and he was discharged as well on the eleventh day in the hospital.

CASE 2.—A Negro girl who was suffering from immediate postpartum atelectasis was given sulfanilamide two days after delivery. A psychosis developed on the next day and was characterized by depression, fearfulness and fear of death for herself and her child. Sulfanilamide was continued, and on the seventh day of this therapy the patient exhibited disorientation for time and place bewilderment, rapid alternation of mood, distractibility and blocking. Further hallucinations were obvious, and she refused to recognize her child. On the following day administration of the drug was stopped; the psychosis disappeared and did not return, in spite of an exacerbation of fever, during which no sulfanilamide was administered. The patient was discharged as entirely well two weeks later.

We conclude that sulfanilamide precipitated a psychosis which promptly disappeared when the drug was withdrawn. Attention should be directed to the necessity of differentiation from a toxic exhaustive psychotic reaction.

DISCUSSION

DR. H. D. PALMER: What was the blood picture in these cases? Did the patients have leukopenia?

DR. MANUEL M. PEARSON: The blood picture in these cases was not one of leukopenia. Danziger also noted the lack of relation between the mental reaction and the blood picture. However, it appears that hypersensitivity to the drug best explains the mental reaction, as it does in reported cases of hemolytic anemia and malignant neutropenia following sulfanilamide therapy.

DR. H. D. PALMER: What was the blood picture in these cases? Did the been based on an individual hypersensitivity or idiosyncracy to the drug, similar to that in patients who show a cutaneous reaction.

FURTHER STUDIES ON METRAZOL THERAPY. DRS. ROBERT S. BOOKHAMMER and MARVIN R. PLESSET, Norristown, Pa. (by invitation).

At the November 1937 meeting of this society, a preliminary report was submitted concerning the use of metrazol in treatment of the psychoses (Bookhammer, Robert S., and Saxe, Earl J.: Preliminary Report on Metrazol Therapy, ARCH. NEUROL. & PSYCHIAT. **39**:864 [April] 1938). We have continued to use this therapy and now present the results in 149 cases.

Table 1 summarizes all the results of treatment. Of special interest is the fact that 52 per cent of all patients showed varying degrees of improvement.

The results for schizophrenia are shown in table 2. Eighty-seven patients in this group were treated. Of these, only 70, or 8 per cent, showed complete remission. Another 8 per cent made a social recovery; 10 per cent were improved, and 74 per cent were unimproved. Of the 14 patients who were greatly improved by treatment, 12 had been ill less than one year. Of the patients who had been ill over two years, 92 per cent failed to respond to therapy.

In table 3 the response to treatment is classified on the basis of the type of schizophrenia. It will be noted that the best response was obtained in patients

TABLE 1.—*Results of Metrazol Treatment in All Cases of Psychoses*

Result	Cases	Percentage
Complete remission	35	23]
Social recovery	22	15 } 52
Improvement	21	14]
No improvement	71	48
	149	

TABLE 2.—*Results of Metrazol Therapy of Schizophrenia*

Result	Total No.	Duration of Illness		
		Up to 1 Yr.	Up to 2 Yr.	Over 2 Yr.
Complete remission	7 (8%)	7 (23%)	0	0
Social recovery	7 (8%)	5 (17%)	0	2 (5%)
Improvement	9 (10%)	4 (13%)	4 (20%)	1 (3%)
No improvement	64 (74%)	14 (47%)	16 (80%)	34 (92%)
	87	30	20	37

TABLE 3.—*Results of Metrazol Treatment of Schizophrenic Psychoses of Various Types*

Result	Simple	Catatonic	Hebephrenic	Paranoid
Complete remission	0	4 (11%)	0	3 (10%)
Social recovery	1 (35%)	4 (11%)	0	2 (6%)
Improvement	0	7 (20%)	1 (5%)	1 (3%)
No improvement	2 (67%)	20 (57%)	17 (95%)	25 (81%)
	3	35	18	31

with the catatonic type (including both stuporous and excited forms) and, to a lesser degree, in patients of the paranoid group. Of 35 patients with the catatonic type, 4 showed complete remission and 4 social recovery. In the paranoid group of 31 patients, 3 had complete remission and 2 social recovery. As can be seen, the response of patients with the hebephrenic type was negligible, with only 1 of 18 showing improvement. Too few patients with the simple type were treated to form a basis for valid conclusions.

In table 4 the results of treatment of patients with manic-depressive psychosis are tabulated. Of 50 treated patients, 22 had a complete remission, only 1 relapse occurring; 12 gained a social recovery, and here too there was 1 relapse. It will be noted that in 16 of the 22 patients with complete remissions the duration of illness was less than one year.

In table 5 the results of treatment are classified as to the type of manic-depressive psychosis. Our results in treating patients with the manic type have not been encouraging, only 1 of 5 showing improvement. The response to treatment of patients with the depressed type was gratifying, however, 93 per cent of this group showing varying degrees of improvement. Of the improved group, 49 per cent had complete remissions, 48 per cent social recovery and 16 per cent improvement. Only 3 patients, or 7 per cent, were not improved. Two patients with the perplexed type were improved.

TABLE 4.—*Results of Metrazol Treatment of Manic-Depressive Psychosis*

Result	Total No.	Duration of Illness			Relapse
		Up to 1 Yr.	Up to 2 Yr.	Over 2 Yr.	
Complete remission	22 (44%)	16 (57%)	5 (36%)	1 (12.5%)	1
Social recovery	12 (24%)	6 (21%)	4 (29%)	2 (25%)	1
Improvement	9 (18%)	3 (11%)	2 (14%)	4 (50%)	1
No improvement	7 (14%)	3 (11%)	3 (21%)	1 (12.5%)	0
	50	28	14	8	3

TABLE 5.—*Results of Metrazol Treatment of Various Types of Manic-Depressive Psychosis*

Result	Manic	Depressed	Perplexed
Complete remission	1 (20%)	21 (49%)	0
Social recovery	0	12 (48%)	0
Improvement	0	7 (16%)	2 (100%)
No improvement	4 (80%)	3 (7%)	0
	5	43	2

TABLE 6.—*Results of Metrazol Treatment of Involutional Psychosis*

Result	Total No.	Duration of Illness		
		Up to 1 Yr.	Up to 2 Yr.	Over 2 Yr.
Complete remission	6 (50%)	4 (50%)	1 (100%)	1 (33%)
Social recovery	3 (25%)	2 (25%)	0	1 (33%)
Improvement	3 (25%)	2 (25%)	0	1 (33%)
No improvement	0	0	0	0
	12	8	1	3

In table 6 are tabulated the results of treatment of involutional psychosis. Of 12 patients, 50 per cent showed complete remission, while the other 50 per cent showed lesser degrees of improvement. Here, again, it is to be pointed out that patients with the earlier forms showed the greater improvement. None in this group were unimproved. There were no relapses.

Summary.—1. The results of convulsion therapy in 149 cases of psychosis are reported. 2. The response of patients with schizophrenia to this treatment has not exceeded the expected rate of recovery of persons not receiving such treatment. 3. The duration of catatonic stupor and excitement is believed to be shortened by the induction of convulsions. 4. This treatment is of value for the depressions of manic-depressive psychosis and for involutional psychoses. 5. In the treatment of this group of patients no serious complications arose, and there were no fatalities.

DISCUSSION

DR. A. P. NOYES: At the Norristown State Hospital there are admitted surprisingly few patients with early schizophrenia, which may account for the fact that these statistics are not more favorable. The best results seem to be secured in cases in which the onset has been stormy, the etiologic factors have been definitely extrinsic and experiential and the patients have been ill less than a year. Results from the use of insulin have been practically the same—much less striking than those reported during the early days of use of this drug.

The results with metrazol in cases of involutional depressions, however, are often almost miraculous. I believe that one does not do justice to a patient with involutional depression, who has no contraindicating physical disease, unless he tries metrazol. The results in the paranoid forms of involutional psychoses are not as gratifying.

DR. M. R. PLESSET: Most of the questions which have arisen have already been discussed. We have been aware of the possibility of vertebral fractures, but in the few cases in which symptoms were referable to the spinal column roentgenographic studies have given normal results. I wish to stress again the value of metrazol therapy in the depressive affective disorders.

ELECTROCARDIOGRAPHIC STUDIES FOLLOWING USE OF METRAZOL. DR. THOMAS K. RATHMELL, Norristown, Pa.

Tracings from psychotic subjects often present artefacts and changes in rate which conform to a distinctive pattern, thus increasing the interpretative difficulties. Particularly with psychotic patients, the problem of damage of cardiac muscle should be approached through a combination of anatomic and functional clinical observations, with data elicited from teleoroentgenographic and electrocardiographic studies. While Hadorn; Heinrich and Sussner; Reese, Vander Veer and Wedge; Dick and McAdam; Lubner, and Pellens have all observed electrocardiographic changes, including acceleration of the rate, sinus tachycardia, extrasystole and temporary heart block, immediately following a metrazol convulsion, my colleagues and I compared electrocardiographic studies before metrazol therapy with those obtained one or two years later.

Fifty-one patients were studied electrocardiographically. In 22 of this group there was no evidence of muscle damage or alteration from the original tracing. There was noted, however, an accelerated rate in 41 patients, sinus tachycardia in 10, wandering pacemaker in 1, sinoauricular block in 1, extrasystole due to an ectopic focus in 1, slurring of the QRS complex in 1, changes in the T_3 wave in 18 and depression of the ST takeoff in 5.

Particular attention was paid to the amplitude of the T waves in lead II. The amplitude of the T_2 waves was not changed in 12 patients and had an average increase of 1.25 mm. in 4 and an average decrease of 1.47 mm. in 35.

The acute changes observed by others were not present in this series, but a large proportion of the group showed acceleration of the cardiac rate, with definite sinus tachycardia, depressions of the ST interval and some lowering of the amplitude of the T waves. The changes noted in the T wave are probably a result of the accelerated rate and are unrelated to the therapy. Acceleration of the rate, particularly a sinus tachycardia which persists for a prolonged period, is not a normal cardiac mechanism. However, I am not willing to attribute even this change to the therapy itself, in view of the role which the nervous system plays in the regulation of the cardiac rate.

It appears that in a fair proportion of cases a so-called normal cardiac system will undergo metrazol therapy without permanent electrocardiographic alteration. Apparently, one or two years after metrazol therapy one may anticipate acceleration of the cardiac rate, or there may be true sinus tachycardia, changes which, if they are a permanent rather than a temporary effect of the nervous system on the cardiac regulatory mechanism at the time of making the tracing, suggest that metrazol may produce changes in the conduction system of the heart.

CHICAGO NEUROLOGICAL SOCIETY

VICTOR E. GONDA, M.D., *President, in the Chair*

Regular Meeting, March 16, 1939

CEREBELLAR TERATOID TUMOR. DR. WILLIAM H. SWEET (by invitation).

A case of teratoid intracranial tumor in which there was an unusual history is reported. A woman aged 54 had had severe headache, vomiting and diplopia for three months, and an unsteady gait, which had become progressively worse, for one and one-half months prior to examination by Dr. G. W. Hall, of Chicago, in January 1926. He found that the patient was disoriented for time and place and had paresis of the facial and palatal muscles on the left side, deviation of the protruded tongue to the left and slight unsteadiness in the heel to knee test bilaterally. Examination of the spinal fluid revealed no cells, a negative Wassermann reaction and a faintly positive Pandy reaction. A diagnosis of glioma of the right cerebral hemisphere was made, but the patient recovered shortly and was apparently well for nine years.

Late in 1935 unsteadiness of gait reappeared, and by the summer of 1936 the patient was unable to walk. The incoordination progressed to involve both upper limbs, and there was incontinence of urine and feces. For one month before admission to the Billings Hospital, in August 1937, she had had dysphagia, and her speech had been slow, slurred and monotonous. Neurologic examination revealed coarse horizontal nystagmus on looking to either side, generalized hypotonia and weakness, ataxia in all four limbs and gross disturbance in cerebration. Roentgenograms of the skull revealed calcification in the posterior part of the posterior cranial fossa, in the midline. The pressure, serologic reactions, cellular content and total protein content of the spinal fluid were normal. The patient died of bilateral pyelonephritis and bronchopneumonia four days after entry.

Postmortem examination of the brain revealed an enormous, multilobulated cystic tumor, occupying the cerebellar vermis and much of each cerebellar hemisphere. At the angle between the inferior surface of the vermis and the caudal end of the fourth ventricle was a mass of tissue forming a nodule in the wall of a cyst. Microscopic examination showed that the cysts were lined by nonsquamous stratified or by columnar epithelium and that the nodule contained a variety of ectodermal and mesodermal tissues—rudimentary hair, smooth muscle, cords of epithelial cells, several glands, fibrous connective tissue, bone and fat.

There was moderate dilatation of the lateral and third ventricles. A striking change was observed in the lamina terminalis; this was greatly thinned, and there was an ostium about 5 mm. in diameter, connecting the third ventricle with the cisterna laminae terminalis. I suggest that the amazing subsidence of the patient's symptoms in 1926 was due to the spontaneous third ventriculostomy at that time resulting from increased pressure in the ventricular system. The patient's history confirms this; in 1925 her symptoms became severe within three months of their onset and were predominantly those of increased intracranial pressure, whereas in 1937 they had developed gradually for two years and were related predominantly to local pressure in the posterior cranial fossa.

DISCUSSION

DR. A. H. VERBRUGGHEN: This case is of great interest to me because of the artificial ventriculostomy. Recently, a young man was admitted to the Presbyterian Hospital in a stuporous state, with paralysis of upward gaze and fixed, dilated pupils, which suggested a tumor in the pineal region. In addition, there was 4 or 5 D. of choking in each eye, with hemorrhages and exudates. The ventriculogram showed a normal pineal recess, making the diagnosis of pineal tumor untenable and indicating clearly that there was a tumor of the midbrain. I happened to return from Ann Arbor, Mich., with Dr. A. E. Walker, who suggested that I perform ventriculostomy and gain time for further examination of the neurologic condition of the patient.

The pituitary gland was approached by the usual frontal flap method; the frontal lobe was elevated and the lamina terminalis identified, and a curved, blunt instrument was inserted into it and spread. The spinal fluid escaped through a reasonably large opening. After this, the choking of the disks disappeared, and the man improved. He was then subjected to a course of roentgen therapy, and almost all neurologic signs disappeared. The rapid disappearance of the tumor with high voltage roentgen therapy suggests that this was a medulloblastoma of the midbrain, even though the patient was 22 years of age.

Dr. Sweet's case of spontaneous ventriculostomy, which was observed by Dr. Walker, no doubt prompted him to suggest the procedure to me; I wish merely to draw attention to the fact that ventriculostomy produced by operation succeeded, as did the spontaneous opening.

Dr. R. P. Mackay: A few years ago I had occasion to study and report the case of a boy aged 4½ years with a tumor similar to this (Ependymoblastoma in the Fourth Ventricle, with New Bone Formation, Arch. Neurol. & Psychiat. **34**:844 [Oct.] 1935). He presented the usual signs of increased intracranial pressure with cerebellar dysfunction. At operation a piece of bone, 2 cm. in diameter, together with about 100 Gm. of tumor, was removed. The patient died the same day. The tumor proved to be an ependymoblastoma and the bone an osteoma in which both intramembranous and intracartilaginous ossification was in progress. No dermal elements were seen. As in Dr. Sweet's case, the neoplasm seemed to be the result of malformation of the median raphe of the nervous system and was classifiable as a teratoma. May I inquire whether the spinal cord was examined in Dr. Sweet's case and, if so, whether any evidences of dysraphia were discovered there.

Dr. Victor Gonda: Was there not some risk in performing a spinal puncture in this case, even though the disks were not choked?

Dr. William H. Sweet: Both grossly and microscopically the spinal cord appeared normal. A spinal puncture was performed after the history was taken and the clinical examination made and before a roentgenogram was taken. If any one knows of a case similar to this, particularly with regard to the spontaneous ventriculostomy, I should appreciate hearing about it.

Behavioral Effects of Lesions of the Frontal Lobe in Man. Dr. Ward C. Halstead (by invitation).

During the past four years, at the University of Chicago Clinics, my associates and I have been analyzing by experimental methods the behavioral effects of lesions of the brain in carefully selected neurosurgical patients, chiefly from the neurologic service of Dr. Percival Bailey. Many of the various experimental situations which we have employed in studying the patients represent adaptations for man of Kluver's method of "equivalent and nonequivalent stimuli." Among the various forms of equivalence which we have examined is one which may be termed equivalence at the level of abstraction. The process of grasping or abstracting essential similarity in the presence of dissimilarity, or the converse, is the essence of normal thinking. Evidence is presented here which indicates that this type of behavior may be impaired in persons with lesions in certain parts of the brain.

Experimental Procedures.—The test objects, in the test situation with which this report is concerned, consist of 62 articles, most of which are familiar or commonplace to the patient. Except for duplicates, the objects of this series differ in such properties as use, shape, size, color, area, mass, "value," material and number. The test procedures are divided into four parts. Part 1 consists of establishing the range of interest in and familiarity of the patient with the test objects. The objects are spread out in random fashion on a table before the patient. He is told to indicate which of the objects have ever been of interest to him. He is permitted to ask questions about any of the objects with which he is not familiar. The examiner notes particularly any evidence of anomia. Part 2 consists of

having the patient make spontaneous groupings of the objects. The objects are again spread out in random fashion before him, and he is told to place together objects which seem to him to "belong together." This general instruction is usually sufficient to start the patient grouping the objects in piles. While he is making his groupings, careful observation is made of the manner in which he proceeds. He is permitted to work without further instruction until he indicates that he has finished. Part 3 consists of testing the patient's memory for the test objects by the method of imminent recall. A cover is placed over the objects on the table, and the patient is asked to mention as many of the objects as he can. He is permitted to continue his efforts to recall the various test objects until he indicates that he can think of no more. At this point he is permitted to rest for from five to ten minutes. Part 4 consists of testing for "abstraction." Step 1: The cover is removed from the test objects, and the patient is told to name each of his groups, i. e., to tell why he placed the objects of any particular group together, such as "metal objects," "colored objects" or "round objects." Step 2: He is then asked, "Is there another way in which you could group them?" This question is repeated after his successive groupings until he indicates that he can think of no further ways of grouping them. Step 3: One after another of his groups is next reestablished on the table by the examiner, who then attempts to enlarge the particular group by including objects omitted by the patient, or the converse. On the basis of his inclusions and exclusions of the additions or subtractions of test objects suggested by the examiner, it is possible to determine whether the level of "abstraction" in dealing with the test objects can be reached by the patient.

There is, however, another phase of the investigation of equivalence which will be reported in detail elsewhere, but which I mention in this connection to emphasize the need for thoroughgoing functional analysis before any but the most tentative conclusions may be safely drawn from work done in this field. This phase is concerned with the definition by progressive analysis of particular forms of equivalence. For this part of the investigation, all the special facilities and materials of a psychologic laboratory are necessary for adequate control of significant variables. In pursuit of the psychologic problem, it has been found necessary to study also a variety of physiologic reactions and to analyze polygraphic records of such concomitants as blood pressure, pulse, galvanic cutaneous response, corneoretinal eye movement potentials and the results of experiments involving controlled projection of special optic and acoustic stimuli.

Results.—The results obtained by applying the foregoing experimental procedures to a group of 11 normal persons ranging in age from 12 to 56 years, to 12 persons with lesions of the posterior part of the brain (outside the frontal lobes) and to 8 persons with lesions of the frontal lobe are summarized in the accompanying table. Of the lesions of the frontal lobe, 6 were in the left frontal lobe, 1 was in the right frontal lobe and 1 (a case of prefrontal agenesis) involved the frontal lobe bilaterally.

It will be noted that for the test situation employed here there is evidence of a difference, both qualitative and quantitative, in the performance of persons with lesions of the brain outside the frontal lobes and that of normal persons. This difference, while in the same direction, is more marked in persons with lesions in the frontal lobes. That this variation from the normal represents a true difference for both types of lesions of the brain is attested by experience in additional cases available since analysis of the first series.

Of particular interest is the fact that there is a marked tendency on the part of normal persons as well as patients with lesions outside the frontal lobes to recall a greater percentage of the test objects which had been grouped than of those that had not been grouped. In some instances this tendency was no less marked when the patient spent approximately twice as much time with the ungrouped as with the grouped objects. This tendency toward preferential recall of the test objects (category effect) may indicate that the organization of a category is such that its content is functionally equivalent, i. e., "equiavailable" for immediate recall. This finding assumes considerable significance in view of some-

what similar studies using affectively or emotionally toned test situations which have led to opposite results. It may preclude the notion, for example, that the affective component in behavior of the type which is here termed equivalence at the level of "abstraction" is always the dominant or controlling factor in immediate recall.

In cases of lesions in the frontal lobes the effect on recall of grouping the test objects (category effect) is absent. This fact, when considered with the paucity of categories, the marked tendency toward fragmentation, the marked resistance in shifting to alternate ways of grouping and the reduced content available for recall, strongly suggests that category behavior at the level of "abstraction" is no longer available to the patient with a lesion of the frontal lobe. Our observations indicate that this is no less true in cases in which the postoperative social adjustment is good, or even unusually good, and in which the "formal intelligence" of the patient (as measured by formal tests) is unaltered after operation.

Results of Equivalence Tests on Normal Persons and Patients with Lesions of the Brain

Subjects	Categories Available	Fragmentation*	Readiness in Shifting†	Percentage of Grouped Objects‡	Number Recalled§	Percentage of Grouped Objects Recalled	Percentage of Ungrouped Objects Recalled	Total Percentage of Recalled Objects
Normal persons.....	14	—	pp	82	41	77	21	68
Patients with posterior lesions of brain.....	10	p—	p—	60	31	71	22	52
Patients with lesions of frontal lobe.....	2	pp	—	34	16	29	23	26

* The qualitative frequency of fragmentation, a form of behavior characterized by the making of "groups" containing only a single object. Here, pp indicates that this behavior was always present; —, that it was never present; p—, that it was present more often than absent, and —p, that it was absent more often than present. The same notation applies to the next column.

† Ease or readiness in shifting, either actively or passively, from one principle to another in grouping the test objects.

‡ Average percentage of the test objects employed by the average patient in his first spontaneous grouping.

§ Average number of objects recalled by the average patient when tested by the method of imminent recall.

That affective components are important factors which contribute to the failure of patients with lesions in the frontal lobe to reach the level of abstraction is revealed by functional analysis of their categories as compared with those of normal persons. Both types of persons have available, for example, a category of "use." For the normal person this category is structured by such subcategories as "apparel," "games" and "tools." In patients with lesions of the frontal lobe a subcategory of "tools" has never been found to be available. In them, equivalence of "use" is available in terms of such devices as completion ("this key has to go in this lock"), reference ("this is my sewing box"), animation ("he buys this and this and this at the ten cent store"), and personification ("these could be pals" or "those kids wouldn't be happy together"). It should be mentioned that we have found category behavior below the level of abstraction to be associated with as many as seven behavioral functions in cases of lesions of the frontal lobe.

Other investigators have reached somewhat similar conclusions concerning the behavioral effects of lesions of the frontal lobe in man. Among these, the studies of Gelb and Goldstein are the most satisfactory from the standpoint of the degree of functional analysis that was reached in the investigation. On the basis of their intensive analyses, these authors concluded that all the general and special symptoms

of frontal lobe deficit are manifestations of a single basic disturbance. Ingenious as were the steps by which this simple formula was evolved, our observations, based on extended study of the best of our material, suggest that this formula is inadequate by virtue of its simplicity. It should be mentioned that, in addition to the fact that we have employed a greater range of test situations, the best of our patients more nearly approximated physiologic preparations than the patients with gunshot injuries of the head who constituted the chief material of the aforementioned investigators.

PICROTOXIN AS A CONVULSANT IN TREATMENT OF CERTAIN ILLNESSES. DRS. A. A. LOW, M. F. BLAUROCK, M. SACHS, C. WADE and E. ROSS.

This paper was published in the April issue of the ARCHIVES, page 747.

DISCUSSION

DR. L. J. POLLOCK: I wish to discuss a feature which perhaps is not germane to the title of the paper but which relates to the remarkable sequence of events of the motor system, as shown in the moving pictures. Picrotoxin has been considered to be one of a group of agents acting as medullary convulsants. In general, the action in lower animals, such as cats, dogs and rabbits, is to produce, first, symptoms referable to the autonomic nervous system of changes in blood pressure and respiration and involuntary urination. The motor manifestations consistently are composed of preconvulsive myoclonic jerks and then of a single clonic seizure or, more commonly, a repetition of them.

I have rarely observed a tonic phase preceding a clonic one in lower animals. From the description of attacks noted in man, it appears that the drug acts on different parts of the nervous system, or that in man, when a convulsion is persistent, other parts of the nervous system participate in the seizure than those involved in lower animals.

DR. R. P. MACKAY: At what time in this sequence of events does consciousness seem to be lost? The isolated jerks prior to the convulsions must be distressing to the patient if consciousness is present.

DR. VICTOR E. GONDA: How do you guard against dislocation of the shoulder? We did not see any protection, nor was any mouth gag shown in the picture.

Whether insulin or metrazol or picrotoxin or some other convulsant does best for these patients is still an open question. Meduna several times expressed his hope that a milder method could be worked out. Already, however, one must be thankful to him for the good results obtained with his method and for the amount of experimental work being done to solve the nature of the so-called functional psychoses. Whether or not this goal will be reached, it is gratifying to see such advances in therapy.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

GILBERT HORRAX, M.D., *Presiding*

Regular Meeting, March 23, 1939

MENINGIOMA "EN PLAQUE" OF THE SPHENOID RIDGE. DR. JAMES L. POPPEN.

The meningiomas as a group, as well as each individual type, have become better understood since publication of the monograph by Cushing and Eisenhardt. In this report I shall include only the meningiomas of the sphenoid wing. Since the symptoms depend greatly on the location of the point of origin on the sphenoid ridge, Cushing classified *en plaque* meningiomas of the sphenoid ridge as deep, middle and pterional.

The deep, or clinoid, tumor usually manifests itself by unilateral diminution of vision, pallor of the optic nerve head and nasal hemianopia. As the tumor

enlarges there are complete blindness on the side involved, with homonymous defect in the other eye, and possibly beginning or frank choking of the optic disk and complete primary atrophy of the optic nerve on the side of the tumor. Exophthalmos occurs with erosion of bone and invasion of the tumor into the retrobulbar space, but may result from pressure on the cavernous sinus and subsequent venous engorgement. Because of the proximity of the superior orbital fissure, varying degrees of oculomotor palsies occur on the side of the lesion. The most common nerve involved is the sixth, although complete ophthalmoplegia may develop. Other signs of local extension may be manifested by olfactory or gustatory hallucinations, mental changes, polydypsia and polyuria and paralysis of the opposite side of the body. Roentgenograms may show erosion or hyperplasia of bone.

The tumor of the middle portion of the sphenoid ridge first manifests itself by evidences of increased intracranial pressure; until the tumor has attained such size that it extends across the midline no symptoms other than mental changes may be noted. Roentgenograms may demonstrate erosion or proliferation, or there may be no change; therefore studies by injection of air must frequently be carried out to verify the site of the tumor.

Of the 19 *en plaque* meningiomas of the pterional region reported by Cushing, all occurred in women; he knew of only 3 cases reported to occur in men. In my group of 10 cases 1 patient was a male. The symptoms are slowly developing exophthalmos with diminished vision on the affected side, swelling in the temporal region, frontal headache and pain in the region of the orbit. Impairment of vision may occur late in the course of the disease; however, the frontal headaches and pain around the eye may be severe early and tend to decrease as the bone continues to thicken. Varying degrees of exophthalmos may be present, depending on the extent of the tumor. The affected eyeball may be only 2 mm., or may be many millimeters, more prominent than the other eyeball. If exophthalmos is marked the conjunctiva is congested and edematous. The exophthalmos is irreducible and nonpulsating, and the eyeball is directed forward and downward. The optic nerve head is pale, with engorgement of the vessels. There may be fulness and tenderness of the temporal muscle (probably due to invasion of the muscle by tumor). Roentgenograms verify the diagnosis, since they demonstrate eburnation of the pterional region. In the very early stages the anteroposterior and posteroanterior views are of particular value.

The hyperostotic effect of these tumors may be great and the production of soft tumor slight, so that in many cases the latter is manifested only by thickened dura with a thin layer of red granular tissure, a few millimeters or more in thickness. A globular tumor was produced in only 1 of my cases. Why meningiomas of this type affect the bone in this way has not been explained. The microscopic appearance of the *en plaque* meningiomas is fairly uniform; in only a few is the bone so densely eburnated that no tumor invasion can be seen.

Even though this type of tumor has been shown to be relatively uncommon, it is one of the most important to recognize and treat early. It is notoriously slow in growth, and therefore considerable hesitancy has been felt by many neurosurgeons in advising early surgical intervention in cases of these growths. Since relatively incomplete removal often gave the patient years of relief, it was considered unwise to perform any radical procedure to remove the tumor. In advanced stages the hazards of radical extirpation increase; as soon as the diagnosis can be made, therefore, wide removal of all the involved bones, as well as the entire sphenoid wing and orbital plate, should be executed.

Since it has been my experience that after surgical treatment of malignant exophthalmic goiter recession of the eyeball is directly proportional to the amount of internal decompression of the orbit, the technic described by Naffziger was modified by removal of the sphenoid wing and the lateral wall of the orbit as well as the orbital plate. As a result of these experiences, the technic now used in removal of the hyperostosing meningiomas of the sphenoid ridge was introduced and systematized.

Briefly, the operation is performed by making a modified coronal incision. The scalp is reflected anteriorly and a frontal osteoplastic bone flap of moderate size is turned down toward the temporal region and broken as low on the temporal

muscle as possible. The dura is separated from the orbital plate posteriorly, well over the greatly thickened sphenoid ridge, optic canal and anterior clinoid process, and also along the temporal bone laterally. The temporal muscle, if not invaded by tumor, is separated from the bone on the lateral surface of the orbit and pterional region. The thickened bone is now removed with giant rongeurs as deeply toward the triangle of the ala magna as possible. The greatly thickened and broad surface is honeycombed with an electric drill, and the interlacing remnants of bone are removed with rongeurs. The orbital plate is then removed with electric drill and rongeurs, care being taken that the orbital capsule is not injured, since if it is unintentionally opened considerable embarrassment is experienced because of the protrusion of fat tissue. Since the inferior and lateral walls of the orbit are greatly thickened in the advanced stages, the burr can again be used to great advantage, the openings being made close to each other so that the partitions left may be readily removed with a rongeur. In this manner all the bone may be removed from the orbital roof, lateral wall and greater sphenoid wing to the superior orbital fissure. The portion of greatly thickened bone which covers the optic foramen and the greatly thickened anterior clinoid process remain. In a few patients the hyperostosis over the anterior clinoid process may resemble a turret and be from 2 to 3 cm. in thickness. If vision is to be restored this bone must be removed; this step naturally is the most hazardous. To remove this portion of bone safely, a special drill, about 2 mm. in diameter, is made with an adjustable sleeve so that the depth can be readily gaged. With this drill attached to the electric motor many small openings, 2 or 3 mm. apart, are made within a few millimeters of the entire thickness of the bone. The greatly weakened structure is then removed with mallet and chisel, small fragments breaking off without much jar or danger of breaking into the sinus. In this manner the entire anterior clinoid process is removed, leaving the superior orbital fissure and optic canal well decompressed. The orbital capsule is then widely opened, and the intraorbital tissues are allowed to protrude. They are examined for the presence of tumor. The incision should start over the ligament of Zinn and pass upward, since in this way the protruding tissues do not interfere with completing the opening of the capsule.

DR. W. J. MIXTER: It is good to have the operation formalized so that one can plan beforehand what to do in a case of this sort. I think it is valuable to have this scheme worked out and presented as a whole.

DR. WALTER R. WEGNER: I wish to ask Dr. Poppen if he can give some idea of the future course in cases of these tumors. Obviously, all the eburnated bone cannot be removed. There is still thickening at the base of the skull and in the roof of the antrum.

DR. GILBERT HORRAX: Dr. Mixter's remarks are much to the point. I remember some of the older cases of Dr. Harvey Cushing at a time when one did not know exactly how to proceed. A certain amount of recession of the eyes, but not very good cosmetic effects, resulted. There was a considerable amount of tumor left, with gradual loss of vision and other symptoms. The main problem is to know exactly what needs to be done, and then as a rule a proper and adequate procedure can be worked out, as has been done with tumors of this type.

DR. J. L. POPPEN: Dr. Wegner is right in asking his question. In the first case especially, there was marked eburnation of the temporal bone. I cannot say what that will lead to later. Many patients live for twenty years without much progress of the disease. The main point is to institute surgical intervention early. If one removes the involved dura, which in a measure is responsible for the hyperostosis, I doubt whether there will be much progress, except possibly for deafness. One patient of Dr. Cushing's was well for many years except for blindness and marked unilateral exophthalmos. I have used the procedure described only in the last three years, so I cannot say much about the patient's future except that it should be satisfactory.

SURGICAL TREATMENT OF EPILEPSY. DRS. W. J. MIXTER and J. C. WHITE.

This paper will be published in full in a later issue of the ARCHIVES.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

JAMES M. STANTON, M.D., *in the Chair*

Regular Meeting, March 23, 1939

MULTIPLE SCLEROSIS AS AN INFECTIOUS DISEASE. DR. GABRIEL STEINER, Detroit.

Pathologically, multiple sclerosis is an encephalomyelitis. This conclusion has been reached by histologic examination of 79 brains and 15 spinal cords, large frozen sections being stained with hematoxylin and eosin, Spielmeyer's method for myelin sheaths, scarlet red for lipids and a special silver stain (the last in 48 cases). In presenting evidence for this conclusion, multiple sclerosis must be considered from three standpoints: (1) as a demyelinating disease of specific type, (2) as a chronic disease and (3) as an encephalomyelitis. The enormous variety in size and shape of the demyelinated plaques, the absence of any limitation to particular structures of the central nervous tissue, the distribution of plaques from the inner (ventricular) and outer (leptomeningeal) surfaces and the lack of involvement of the peripheral nerves are evidences of a peculiar and uniform type of demyelinating disease. The concomitant presence of old, more recent and fresh plaques ("heterophasic" appearance) indicates the chronic and progressive character of the disease. The inflammatory process runs parallel with the acute or subacute stage of multiple sclerosis and with the acute stage of a single plaque. In old plaques of an inactive type inflammatory lesions have disappeared. Thus, a primary inflammatory character of multiple sclerosis is indicated, and the disease must be considered encephalomyelitis. The cause of primary inflammatory diseases of the central nervous system is almost always an infection. Clinically at least six items support the theory of an infectious rather than an endogenous or heredodegenerative origin of multiple sclerosis: the clinical multiformity and variability of the disease, the fluctuating course, the frequent initial appearance with monosymptomatic disorders of the cranial nerves, the peculiar regional distribution, the difference in occupational incidence, the changes in the cerebrospinal fluid in acute attacks and a new specific hemicserologic reaction (Sachs and Steiner).

Definite proof of the infectious origin of multiple sclerosis cannot be found by means of clinical research or neuropathologic or serologic investigations but can be obtained only by direct parasitologic examination. A special method has been developed, therefore, to stain bacteria and spirochetes in large frozen sections. By this method phagocytic cells can be demonstrated in the brain and other organs in different diseases of well known spirochetal origin (syphilis, relapsing fever, Weil's disease). Similar phagocytic cells filled with argyrophilic debris were seen in recent plaques of multiple sclerosis in each of 48 brains and spinal cords examined. Of course, the presence of phagocytes containing argyrophilic debris does not prove the spirochetal origin of a disease. It may be considered as a clue that there remains some of a foreign substance which has been taken up by phagocytes. Finally, however, the spirochetes themselves were demonstrated. They were of different type from the Spirochaeta pallida. These organisms were located in the plaques in which there were recent and stormy catabolic processes, usually in the parenchyma of peripheral portions of the plaques or in the adventitial walls of blood vessels. The demonstration of spirochetes with this method has been confirmed by Rogers in 1 of 11 cases and by Scheinker in 4 of 8 cases. I consider the finding of spirochetes in the brain and spinal cord in cases of multiple sclerosis as an initial step toward better knowledge of the etiologic factors.

ELECTROENCEPHALOGRAPHY. DR. S. STEPHEN BOHN.

The results of electroencephalographic examination of the first 100 patients were reviewed. The apparatus used was a capacity-coupled, push-pull, double channel amplifier, with ink writers capable of transmitting frequencies up to 80

cycles per second without distortion. The speed of the moving paper was 30 mm. per second. The electrodes consisted of lumps of solder, 5 mm. in diameter, and were held in place by means of collodion. Indifferent electrodes were placed on the lobes of the ears, while active electrodes during a routine examination of the head were placed just off the midline on either side, at points corresponding to the prefrontal, motor, parietal and occipital areas. When additional information was necessary, electrodes were also placed over the temporal area and the cerebellar region. When an intracranial lesion, such as a tumor of the brain, was being localized, many more active electrodes were applied on the side of the lesion.

No definite conclusions were offered concerning this work, but the histories of several patients were read, and the electroencephalographic tracings were shown on a screen. The belief was expressed, first, that tumors of the brain can be localized by this means; second, that patients with migraine headaches show brain waves differing from the normal in form and frequency and, to a lesser extent, in voltage. The results of electroencephalographic examination in cases of idiopathic paroxysmal convulsive states by other observers were reviewed. Finally, the records of patients with functional mental disorders, as well as of those with organic nonmental disease, were compared. Many patients with psychoneuroses were found to have brain waves similar to those in organic neurologic conditions, such as tumor of the brain. Some of the patients showed fluctuations in the amplitude, shape and form of waves on being questioned, especially in regard to vital points in their histories.

The belief was expressed that electroencephalography will have a useful place as an adjunct and that it should be used in the same way as regular laboratory examinations. At no time has this procedure misled the examiner in making a diagnosis from false localizing signs.

Book Reviews

Der jugendliche Schwachsinn: Seine Erkennung, Behandlung und Ausmerzung. By Wilhelm Weygandt. Price: Cloth, 30 marks; paper, 28 marks. Pp. 426, with 159 illustrations. Stuttgart: Ferdinand Enke, 1936.

To the reviewer's knowledge, this is Weygandt's last book. Soon after its publication the author died. Unfortunately, it must be said that the last production mars an otherwise brilliant scientific record. The book is meant to be an enthusiastic endorsement of the law of 1933 for the prevention of hereditary diseases (*Gesetz zur Verhütung erbkranken Nachwuchses*). It is only fair to state that Weygandt was in favor of such a law long before the Nazis came into power. However, while his previous publications were noted for moderation in tone and objectivity in presenting evidence, the present exposition is marked by a spirit of propaganda and by conspicuous subjectivity. There is too much effort to prove a point against the available evidence. The remarkable thing is that the counter-evidence is, nevertheless, fully presented. After several authors are quoted as estimating that at most in two thirds of all cases mental deficiency is hereditary in nature, Weygandt gives his own estimate as 90 per cent, without offering new supporting data. He discusses the cases of Laura Bridgman and Helen Keller as examples of deaf-mutism and blindness which were obviously due to exogenous factors and adds the arbitrary remark that in "perhaps half of the cases" the condition is hereditary and congenital. Goddard's Kallikak family and Dugdale's Juke family, long since proved to be examples of uncritical statistical sleight of hand, are trotted out again in proof of family degeneration over many successive generations. That cryptogenic epilepsy not only is hereditary but has a particularly strong hereditary striking power (*besondere Durchschlagkraft der erblichen Belastung*) is offered as dogma without attempt at substantiation. That malformation may be due to intrauterine inflammations and amputations is admitted. Yet, "most malformations must be considered as hereditarily determined." That schizophrenia is a "recessively transmitted mental disease" is taken for granted. The author regrets that prior to 1933 persons who had previously been committed to hospitals for mental disease were permitted to marry. The new law exempts hysterical persons from sterilization. However, Weygandt recommends that the law, if revised, should be extended to include "persons with severe hysteria." Aside from its strong emphasis on heredity and its fanatic advocacy of surgical prevention of feeblemindedness, mental disease and "devious reactions," the book offers nothing essentially new in its treatment of the subject matter. In its descriptive parts it is efficient and sound, but adds nothing that cannot be conveniently found in the well known texts.

News and Comment

THE MENNINGER CLINIC

The Menninger Clinic offers four accredited residencies annually, two beginning January 1 and two July 1. Intensive training is given in psychoanalytic psychiatry, neurology, child psychiatry and psychotherapeutic and other psychiatric technics. Applications for openings in July 1940 are now being received. Address: The Menninger Sanitarium, Topeka, Kan.